10813347

=> d his

(FILE 'HOME' ENTERED AT 19:10:40 ON 17 SEP 2004)

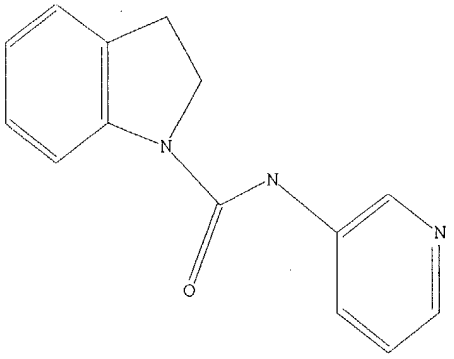
FILE 'REGISTRY' ENTERED AT 19:10:51 ON 17 SEP 2004
L1 STRUCTURE UPLOADED
L2 5 S L1
L3 248 S L1 SSS FULL

FILE 'CAPLUS' ENTERED AT 19:12:06 ON 17 SEP 2004
L4 107 S L3
L5 62 S L4 AND SEROTONIN

FILE 'REGISTRY' ENTERED AT 19:15:12 ON 17 SEP 2004
L6 STRUCTURE UPLOADED
L7 2 S L6 SUB=L3 SAMPLE
L8 118 S L6 SSS FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 19:16:46 ON 17 SEP 2004
L9 59 S L8
L10 2 S L7
L11 57 S L9 NOT L10
L12 57 S L11 NOT PYRROLOQUINOLIN?
L13 27 S L11 AND THU/RL
L14 13 S L13 AND PATENT/DT
L15 23 S L13 AND (SEROTONIN OR 5-HT)

=> d l1
L1 HAS NO ANSWERS
L1 STR



10813347

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L14 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:1007134 CAPLUS
DN 140:53411
TI Immunomodulation and effect on cell processes relating to serotonin family receptors and the blood-brain barrier
IN Jameson, Bradford A.; Tretiakova, Anna A.; Davidson, Harold Carter
PA Philadelphia Health and Education Corporation, USA
SO PCT Int. Appl., 208 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003106660	A2	20031224	WO 2003-US19595	20030617
	WO 2003106660	A3	20040617		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

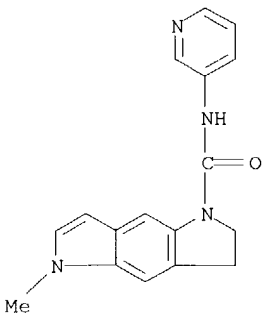
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 2002-389577P	P	20020617
	US 2002-414831P	P	20020927

AB The invention relates to the discovery that signaling via a serotonin type 1B, 2, 4 and 6 receptor is important in T cell activation and that inhibiting this signaling, such as by using fluphenazine, can be used to modulate the immune response, cell proliferation, and apoptosis, among other cell processes. This immunomodulation is useful for the treatment of immune diseases or conditions, and for the development of potential therapeutics for such diseases or conditions. It has been further discovered that, in cells proceeding through the cell cycle process, inhibition of serotonin signaling inhibits the process and induces apoptosis and morphol. changes to a cell. These effects of inhibiting serotonergic signaling can be useful for effecting selective cell killing and for identifying compds. that inhibit the signaling. Addnl., methods for the use, identification and production of an inhibitor that does not substantially cross the blood-brain barrier are also provided.

IT **158942-04-2**, SB 206553
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(immunomodulation and effect on cell processes relating to serotonin family receptors and blood-brain barrier)

RN 158942-04-2 CAPLUS
CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



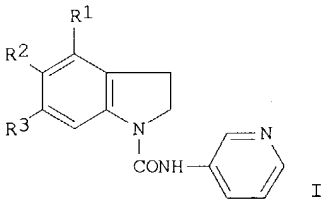
L14 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:771372 CAPLUS
DN 139:276822

10813347

TI Preparation of pyridinylcarbamoylindolines as 5-HT2C antagonists
IN Lavielle, Gilbert; Muller, Olivier; Millan, Mark; Gobert, Alain
PA Les Laboratoires Servier, Fr.
SO Eur. Pat. Appl., 4 pp.
CODEN: EPXXDW
DT **Patent**
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1348704	A1	20031001	EP 2003-290759	20030326
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	FR 2837823	A1	20031003	FR 2002-3788	20020327
	NO 2003001371	A	20030929	NO 2003-1371	20030326
	NZ 524958	A	20040326	NZ 2003-524958	20030326
	CN 1446813	A	20031008	CN 2003-121184	20030327
	US 2003199555	A1	20031023	US 2003-400358	20030327
	US 6759421	B2	20040706		
	JP 2004035541	A2	20040205	JP 2003-86786	20030327
PRAI	FR 2002-3788	A	20020327		

OS MARPAT 139:276822
GI

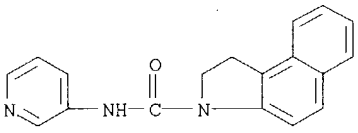


I

AB Title compds. I [R1R2 = (un)substituted CH:CHCH:CH, R3 = H; R1 = H, R2R3 = (un)substituted CH:CHCH:CH] were prepared for use as 5-HT2C antagonists in treatment of diseases, such as depression, anxiety, impulsive disorders, schizophrenia, Parkinson's disease, migraine, cognitive disorders, sexual dysfunction, sleep disorders, bulimia, and anorexia. Thus, 4-ClC6H4OCH2CN was treated with 2-nitronaphthalene, and reduced in two steps to 2,3-dihydro-1H-benz[e]indole which was treated with nicotinoyl azide to give I [R1R2 = CH:CHCH:CH, R3 = H]. This compound at 10 mg/kg orally in rats inhibited penile erections stimulated by 1.25 mg/kg s.c. Ro 60-0175 by 100%.

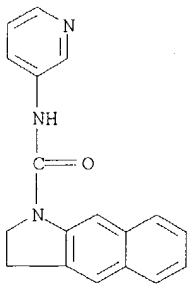
IT **606937-67-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyridinylcarbamoylindolines as 5-HT2C antagonists)

RN 606937-67-1 CAPLUS
CN 3H-Benz[e]indole-3-carboxamide, 1,2-dihydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



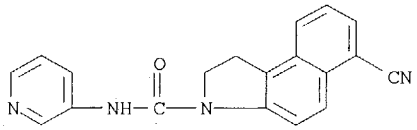
IT **606937-68-2P 606937-69-3P 606937-70-6P**
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyridinylcarbamoylindolines as 5-HT2C antagonists)

RN 606937-68-2 CAPLUS
CN 1H-Benz[f]indole-1-carboxamide, 2,3-dihydro-N-3-pyridinyl-, monohydrochloride (9CI) (CA INDEX NAME)



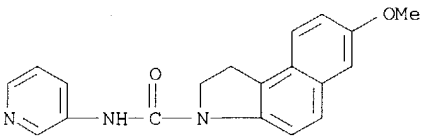
● HCl

RN 606937-69-3 CAPLUS
CN 3H-Benz[e]indole-3-carboxamide, 6-cyano-1,2-dihydro-N-3-pyridinyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 606937-70-6 CAPLUS
CN 3H-Benz[e]indole-3-carboxamide, 1,2-dihydro-7-methoxy-N-3-pyridinyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:570643 CAPLUS
DN 139:111697
TI Method of increasing milk production
IN Horseman, Nelson D.
PA USA
SO U.S. Pat. Appl. Publ., 16 pp.
CODEN: USXXCO
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003139420	A1	20030724	US 2003-351474	20030122
PRAI	US 2002-351134P	P	20020123		

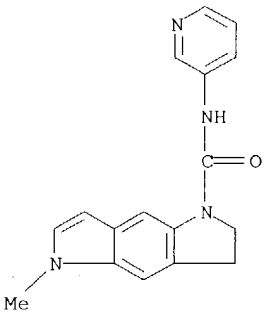
AB The invention relates generally to the use of pharmaceutical compns. to increase milk production alone or in combination with certain biol. active

ingredients. Specifically, the method relates to the use of pharmaceutical compns. that will act on the feedback of the intrinsic regulatory pathway in the mammalian mammary gland. The present invention provides for as a method of increasing bovine milk production as well as a method of correcting certain human lactation abnormalities. Preferably, the compds. used in the methods of the present invention are one or more active agents capable of inhibiting peripheral aromatic amino acid decarboxylase enzymes, peripheral tryptophan hydroxylase enzymes, peripheral serotonin enzymes, or a combination of enzymes thereof.

IT **158942-04-2,** SB 206553
RL: AGR (Agricultural use); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(method of increasing milk production)

RN 158942-04-2 CAPLUS

CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



L14 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:532342 CAPLUS

DN 139:95476

TI Agents having serotonin-related pharmacol. activity for the pharmacological treatment of sleep apnea and other sleep-related breathing disorders

IN Radulovacki, Miodrag; Carley, David W.

PA USA

SO U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U.S. Ser. No. 16,901.
CODEN: USXXCO

DT **Patent**

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003130266	A1	20030710	US 2002-285277	20021031
	US 2002086870	A1	20020704	US 2001-16901	20011214
	US 6727242	B2	20040427		
	WO 2004041272	A2	20040521	WO 2003-US34592	20031029
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	US 2001-16901	A2	20011214		
	US 1998-76216P	P	19980227		
	WO 1999-US4347	W	19990226		
	US 2000-622823	A1	20000823		
	US 2002-285277	A	20021031		

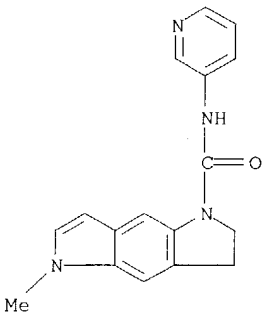
AB The invention discloses pharmacol. methods for the prevention of amelioration of sleep-related breathing disorders via administration of agents or combinations of agents that possess serotonin-related pharmacol. activity. Agents of the invention include e.g. ondansetron.

IT **158942-04-2D,** SB-206553, quaternized

RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(agents with serotonin-related pharmacol. activity for treatment of sleep apnea and other sleep-related breathing disorders)

RN 158942-04-2 CAPLUS

CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



L14 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:777665 CAPLUS

DN 137:273197

TI Immunomodulation and effect on cell processes relating to serotonin family receptors

IN Jameson, Bradford A.; Tretiakova, Anna S.; Albert, Ross; Davidson, Harold Carter

PA Philadelphia Health and Education Corporation, USA

SO PCT Int. Appl., 172 pp.
CODEN: PIXXD2

DT **Patent**

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002078643	A2	20021010	WO 2002-US9993	20020329
	WO 2002078643	A3	20040122		
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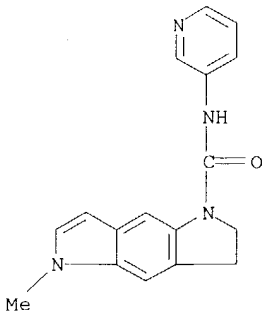
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003100570	A1	20030529	US 2002-112261	20020329
	EP 1401410	A2	20040331	EP 2002-733924	20020329
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2001-280296P	P	20010330		
	US 2001-345295P	P	20011025		
	US 2002-353883P	P	20020131		
	WO 2002-US9993	W	20020329		

AB The present invention relates to the discovery that signaling via a serotonin type 1B, 2, 4 and 6 receptor is important in T cell activation such that inhibiting such signaling can be used to modulate the immune response. This immunomodulation is useful for the treatment of immune diseases or conditions, and for the development of potential therapeutics for such diseases or conditions. It has been further discovered that, in cells proceeding through the cell cycle process, inhibition of serotonin signaling inhibits the process and induces apoptosis and morphol. changes to a cell. These effects of inhibiting serotonergic signaling can be useful for effecting selective cell killing and for identifying compds. that inhibit the signaling.

IT **158942-04-2**, SB206553
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(immunomodulation and effect on cell processes relating to serotonin family receptors)
RN 158942-04-2 CAPLUS
CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



L14 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:759601 CAPLUS
DN 135:303774
TI Synthesis of cyclobuta-indole-carboxamide derivatives and their use as CNS agents
IN Peglion, Jean-Louis; Goument, Bertrand; Millan, Mark; Lejeune, Francoise; Cussac, Didier
PA Adir Et Compagnie, Fr.; Les Laboratoires Servier
SO Eur. Pat. Appl., 33 pp.
CODEN: EPXXDW
DT **Patent**
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1146044	A1	20011017	EP 2001-400939	20010412
	EP 1146044	B1	20040901		
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	BR 2001001466	A	20011211	BR 2001-1466	20010411
	NZ 511091	A	20010928	NZ 2001-511091	20010412
	CA 2344108	AA	20011013	CA 2001-2344108	20010412
	ZA 2001003064	A	20011018	ZA 2001-3064	20010412
	JP 2001302661	A2	20011031	JP 2001-114261	20010412
	JP 3396675	B2	20030414		
	US 2001044426	A1	20011122	US 2001-833826	20010412
	US 6452015	B2	20020917		
	CN 1323796	A	20011128	CN 2001-116387	20010413
	US 2003032812	A1	20030213	US 2002-195009	20020712
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	US 2001-833826	A3	20010412		

OS MARPAT 135:303774
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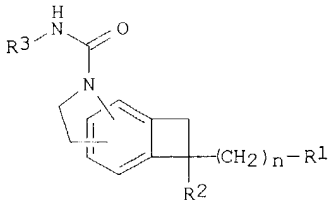

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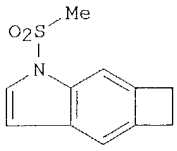
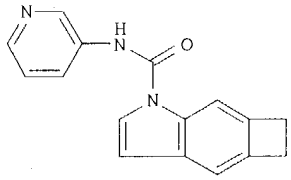


II



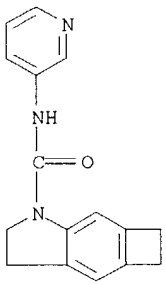
III

AB Title compds. I [n = 0 - 6; R1 = H, OH, CN, alkoxy(carbonyl), carboxy, aminocarbonyl, etc.; R2 = H, alkyl, hydroxymethyl, etc.; R3 = H, alkyl, aryl, heteroaryl] were prepared Twelve examples were provided. E.g., 4-[(2,2-dimethoxyethyl)amino]benzocyclobutane (preparation given) was converted to the N-methanesulfonyl derivative (Pyridine, MsCl) and cyclized to indole II (TiCl4, PhMe). II was deprotected and reduced (i. KOMe, MeOH, reflux, ii. HOAc, NaCNBH3, 2 h, room temperature) to the 2,3,5,6-tetrahydroindole derivative and treated with a solution of nicotinoyl azide (that had been thermally decomposed to the isocyanate) by heating in toluene to give III. In animal models predictive of antidepressant activity, III was effective at a dose of 2.5 mg/kg s.c. (mice). I are used to treat depression, obsessive-compulsive disorder, anxiety, etc.

IT **367263-93-2P 367263-94-3P 367263-95-4P 367263-96-5P 367263-97-6P 367263-98-7P 367263-99-8P 367264-00-4P 367264-01-5P 367264-03-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug; synthesis of cyclobuta-indole-carboxamide derivs. and their use as CNS agents)

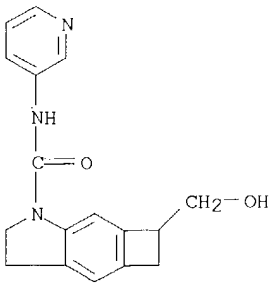
RN 367263-93-2 CAPLUS

CN 1H-Cyclobut[f]indole-1-carboxamide, 2,3,5,6-tetrahydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)

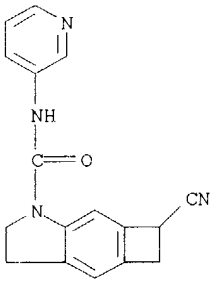


RN 367263-94-3 CAPLUS

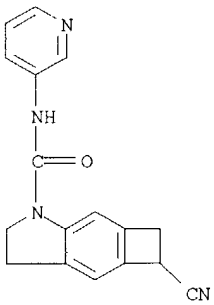
CN 1H-Cyclobut[f]indole-1-carboxamide, 2,3,5,6-tetrahydro-6-(hydroxymethyl)-N-3-pyridinyl- (9CI) (CA INDEX NAME)



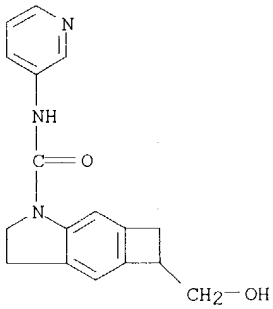
RN 367263-95-4 CAPLUS
CN 1H-Cyclobut[f]indole-1-carboxamide, 6-cyano-2,3,5,6-tetrahydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



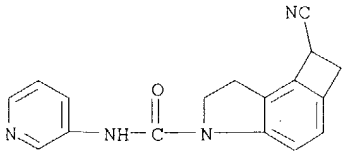
RN 367263-96-5 CAPLUS
CN 1H-Cyclobut[f]indole-1-carboxamide, 5-cyano-2,3,5,6-tetrahydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



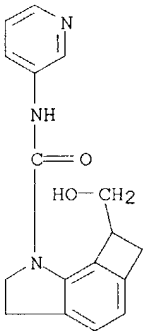
RN 367263-97-6 CAPLUS
CN 1H-Cyclobut[f]indole-1-carboxamide, 2,3,5,6-tetrahydro-5-(hydroxymethyl)-N-3-pyridinyl- (9CI) (CA INDEX NAME)



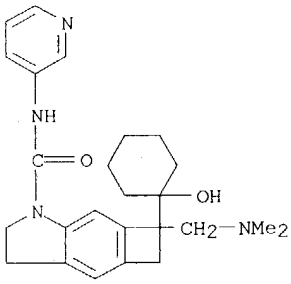
RN 367263-98-7 CAPLUS
CN 3H-Cyclobut[e]indole-3-carboxamide, 7-cyano-1,2,6,7-tetrahydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



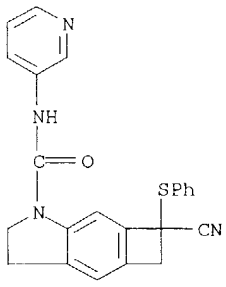
RN 367263-99-8 CAPLUS
CN 1H-Cyclobut[g]indole-1-carboxamide, 2,3,6,7-tetrahydro-7-(hydroxymethyl)-N-3-pyridinyl- (9CI) (CA INDEX NAME)



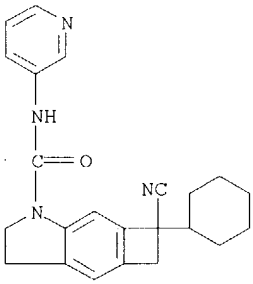
RN 367264-00-4 CAPLUS
CN 1H-Cyclobut[f]indole-1-carboxamide, 6-[(dimethylamino)methyl]-2,3,5,6-tetrahydro-6-(1-hydroxycyclohexyl)-N-3-pyridinyl- (9CI) (CA INDEX NAME)



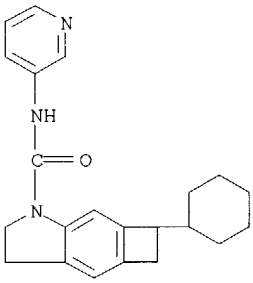
RN 367264-01-5 CAPLUS
CN 1H-Cyclobut[f]indole-1-carboxamide, 6-cyano-2,3,5,6-tetrahydro-6-(phenylthio)-N-3-pyridinyl- (9CI) (CA INDEX NAME)



RN 367264-03-7 CAPLUS
CN 1H-Cyclobut[f]indole-1-carboxamide, 6-cyano-6-cyclohexyl-2,3,5,6-tetrahydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



IT **367264-05-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; synthesis of cyclobuta-indole-carboxamide derivs. and their use as CNS agents)
RN 367264-05-9 CAPLUS
CN 1H-Cyclobut[f]indole-1-carboxamide, 6-cyclohexyl-2,3,5,6-tetrahydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:564823 CAPLUS
DN 135:132455
TI Composition for treatment of stress
IN Wurtman, Judith J.; Wurtman, Richard J.
PA Massachusetts Institute of Technology, USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001054681	A2	20010802	WO 2001-US2854	20010129
	WO 2001054681	C1	20020117		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6579899	B1	20030617	US 2000-492110	20000127

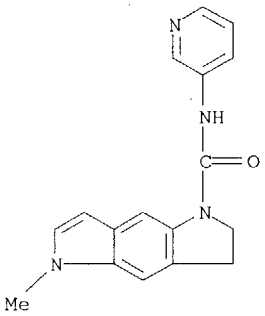
	EP 1253915	A1	20021106	EP 2001-905173	20010129
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003521498	T2	20030715	JP 2001-555659	20010129
PRAI	US 2000-492110	A2	20000127		
	US 1998-93013P	P	19980716		
	US 1999-354738	B2	19990716		
	WO 2001-US2854	W	20010129		

AB A method of treating stress in a patient showing stress related symptoms is disclosed, where the method comprises administering to the patient an effective amount of a serotoninergic drug or prodrug. Specific examples of such drugs are described, and include, among others, tryptophan or 5-hydroxytryptophan, or their salts.

IT **158942-04-2,** SB 206553
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(composition for treatment of stress using serotoninergic drugs or prodrugs)

RN 158942-04-2 CAPLUS

CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



L14 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:434808 CAPLUS

DN 135:41033

TI The combination of a serotonin reuptake inhibitor and a 5-HT2C antagonist, inverse agonist or partial agonist

IN Cremers, Thomas Ivo Franciscus Hubert; Wikstroem, Hakan Wilhelm; Den Boer, Johan Antonie; Bosker, Fokko Jan; Westerink, Bernard Hendrik Cornelis; Bogeso, Klaus Peter; Hogg, Sandra; Mork, Arne

PA H. Lundbeck A/s, Den.

SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2

DT **Patent**

LA English

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001041701	A2	20010614	WO 2000-DK671	20001206
WO 2001041701	A3	20011213		
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001018511	A5	20010618	AU 2001-18511	20001206
US 2002103249	A1	20020801	US 2000-731411	20001206
EP 1237553	A2	20020911	EP 2000-981174	20001206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
TR 200201512	T2	20020923	TR 2002-200201512	20001206
BR 2000016385	A	20030218	BR 2000-16385	20001206

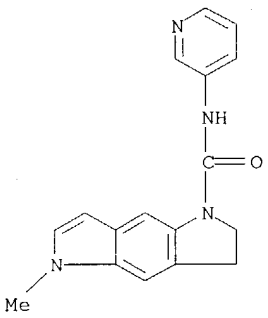
	JP 2003516326	T2	20030513	JP 2001-542871	20001206
	EP 1396267	A2	20040310	EP 2003-27672	20001206
	EP 1396267	A3	20040421		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	NO 2002002657	A	20020726	NO 2002-2657	20020605
	US 2003032636	A1	20030213	US 2002-165196	20020606
	BG 106895	A	20030430	BG 2002-106895	20020702
PRAI	US 1999-169245P	P	19991206		
	EP 2000-981174	A3	20001206		
	WO 2000-DK671	W	20001206		

AB The present invention relates to the use of compds. and compns. of compds. having serotonin reuptake inhibiting activity and 5-HT2C antagonistic, partial agonistic or inverse agonistic activity for the for the treatment of depression and other affective disorders. The combined serotonin reuptake inhibiting effect and the 5-HT2C antagonistic, partial agonistic or inverse agonistic effect may reside within the same chemical compound or in two different chemical compds. E.g., simultaneous administration of 10 μmol/kg citalopram with 1 μmol/kg RS 102221 or Lu 27121 showed significant enhancement of the effect of citalopram in rats.

IT **158942-04-2,** SB 206553
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(combination of a serotonin reuptake inhibitor and a 5-HT2C antagonist, inverse agonist or partial agonist)

RN 158942-04-2 CAPLUS

CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



L14 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:68328 CAPLUS

DN 132:117552

TI Composition and method using serotoninergic drug for treatment of stress

IN Wurtman, Judith J.; Wurtman, Richard J.

PA Massachusetts Institute of Technology, USA

SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2

DT **Patent**

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000003701	A1	20000127	WO 1999-US16153	19990716
	W: CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2337507	AA	20000127	CA 1999-2337507	19990716
	EP 1096927	A1	20010509	EP 1999-934107	19990716
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002520353	T2	20020709	JP 2000-559836	19990716
PRAI	US 1998-93013P	P	19980716		
	WO 1999-US16153	W	19990716		

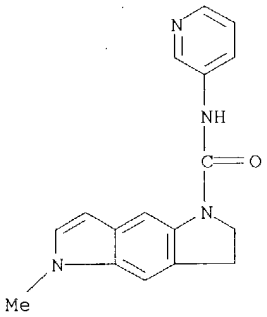
AB A method of treating stress in a patient showing stress-related symptoms comprises administering to the patient an effective amount of a serotoninergic drug. Specific examples of this class of drugs are described, and include as examples, among others, the use of lithium, chlorimipramine, fluoxetine, fluvoxamine, sertraline, MK-212, Ro

60-0332/ORG 35035, Ro 60-175/ORG 35030, d,l-fenfluramine, dexfenfluramine, or a salt thereof.

IT **158942-04-2**, SB 206553
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(serotoninergic drug for treatment of stress)

RN 158942-04-2 CAPLUS

CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:565907 CAPLUS

DN 131:194295

TI Agents, and combinations thereof, with serotonin-related activity for the treatment of sleep-related breathing disorders

IN Radulovacki, Miodrag; Carley, David W.

PA The Board of Trustees of the University of Illinois, USA

SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

DT **Patent**

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9943319	A1	19990902	WO 1999-US4347	19990226
	W: CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2321900	AA	19990902	CA 1999-2321900	19990226
	EP 1066036	A1	20010110	EP 1999-909664	19990226
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002504510	T2	20020212	JP 2000-533116	19990226
	US 6331536	B1	20011218	US 2000-622823	20000823
	US 2002086870	A1	20020704	US 2001-16901	20011214
	US 6727242	B2	20040427		
PRAI	US 1998-76216P	P	19980227		
	WO 1999-US4347	W	19990226		
	US 2000-622823	A1	20000823		

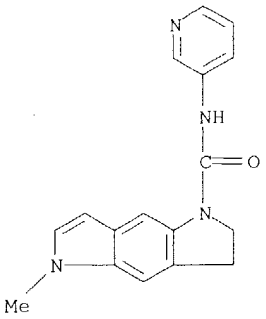
AB Pharmacol. methods are provided for the prevention or amelioration of sleep-related breathing disorders via administration of agents or combinations of agents that possess serotonin-related pharmacol. activity.

IT **158942-04-2**, SB-206553
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(agents, and combinations thereof, with serotonin-related activity for treatment of sleep-related breathing disorders)

RN 158942-04-2 CAPLUS

CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)

10813347

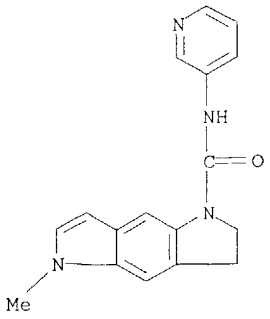


RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:98347 CAPLUS
DN 128:176168
TI Pharmaceutical compositions containing a 5-HT2C antagonist and a D2 antagonist for treatment of CNS disorders, including schizophrenia, and compound preparation
IN Blackburn, Thomas Paul
PA Smithkline Beecham PLC, UK; Blackburn, Thomas Paul
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9804289	A2	19980205	WO 1997-EP4159	19970722
	WO 9804289	A3	19980319		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2261813	AA	19980205	CA 1997-2261813	19970722
	AU 9742972	A1	19980220	AU 1997-42972	19970722
	AU 725817	B2	20001019		
	BR 9710568	A	19990817	BR 1997-10568	19970722
	EP 936924	A2	19990825	EP 1997-918947	19970722
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
	CN 1230894	A	19991006	CN 1997-197977	19970722
	NZ 333813	A	20000728	NZ 1997-333813	19970722
	JP 2000516924	T2	20001219	JP 1998-508522	19970722
	ZA 9706593	A	19990125	ZA 1997-6593	19970724
	NO 9900322	A	19990324	NO 1999-322	19990125
	KR 2000029564	A	20000525	KR 1999-700622	19990125
PRAI	GB 1996-15767	A	19960726		
	WO 1997-EP4159	W	19970722		

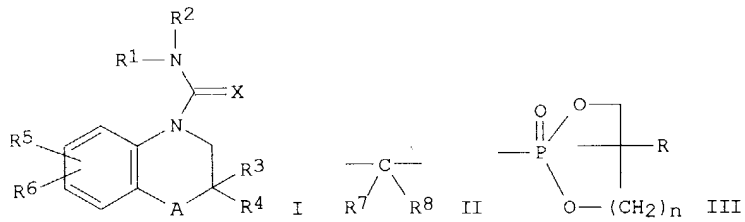
AB Combinations of compds. having 5-HT2C and D2 antagonist activity, compds. having activity at the two receptors, pharmaceutical compns. containing them, and their use in treating CNS disorders, including schizophrenia, are disclosed.
IT **158942-04-2,** SB-206553
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use);** BIOL (Biological study); USES (Uses)
(D2 antagonist and 5-HT2C antagonist for treatment of CNS disorders, including schizophrenia, and compound preparation)
RN 158942-04-2 CAPLUS
CN Benzo[1,2-b:4,5-b']dipyrrole-1(2H)-carboxamide, 3,5-dihydro-5-methyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



L14 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:350452 CAPLUS
DN 125:114508
TI Aminocarbonyl (thiocarbonyl) and cyanoguanidine derivatives of quinoline and indoline
IN Atwal, Karnail S.; Ferrara, Francis N.
PA E. R. Squibb and Sons, Inc., USA
SO U.S., 13 pp., Cont.-in-part of U.S. Ser. No. 977,340, abandoned.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5514690	A	19960507	US 1993-111239	19930824
	EP 610553	A1	19940817	EP 1993-117267	19931025
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	AU 9350653	A1	19940602	AU 1993-50653	19931112
	JP 06228092	A2	19940816	JP 1993-284924	19931115
PRAI	US 1992-977340		19921117		

OS MARPAT 125:114508
GI

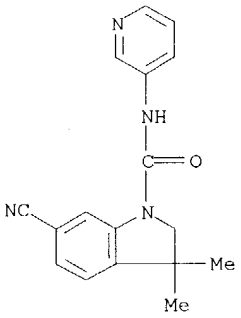


AB Novel compds. having potassium channel activating activity and useful, for example, as antiischemic agents are disclosed. These compds. have the general formula I, where A is II or a single bond to complete an indoline nucleus; X is -O-, -S- or -NCN; R1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl group; R2 is H, alkyl, or arylalkyl group or R1 and R2 form a 5-7 membered saturated or unsatd. ring which may further include an aryl group fused to 2 C atoms of the ring; R3, R4, R7, R8 are H, alkyl, or arylalkyl group or R3 and R4 and/or R7 and R8 including the C atom connecting them form a 5-7 membered carbocyclic ring when A is II and R7 and R8 are not H and R3 and R4 are H or R7 and R8 are H and R3 and R4 are not H; R5 is H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl arylalkyl, (cycloalkyl)alkyl, -CN, -NO2, -COR, -COOR, -CONHR, -CON(R)2, -CF3, -S-alkyl, -SOalkyl, SO2alkyl, -PO(Oalkyl)2, III, halogen, amino, substituted amino, -Oalkyl, -OCF3, -OCH2CF3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl, -NRCOOalkyl, or -NRCON(R)2 with R being H, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl; and R6 is H, alkyl, halo, _OH, amino, substituted amino, -Oalkyl, -OCOalkyl, -OCONRalkyl, -NRCOalkyl, -NRCOOalkyl, or -NRCON(R)2; n is 1, 2, or 3; and when A is a single bond and R1 is aryl, R3 and R4 are both alkyl.

IT **158326-73-9P**

RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure and manufacture of aminocarbonyl (thiocarbonyl) and cyanoguanidine derivs. of quinoline and indoline for antiischemic agent)

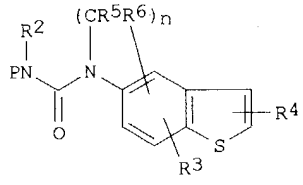
RN 158326-73-9 CAPLUS
CN 1H-Indole-1-carboxamide, 6-cyano-2,3-dihydro-3,3-dimethyl-N-3-pyridinyl- (9CI) (CA INDEX NAME)



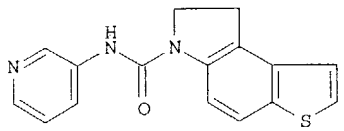
L14 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:252512 CAPLUS
DN 122:31572
TI Thienoindole derivatives as 5-HT2c and 5-HT2b antagonists
IN Forbes, Ian Thomson; Martin, Roger Thomas; Jones, Graham Elgin
PA Smithkline Beecham PLC, UK
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9422871	A1	19941013	WO 1994-EP917	19940322
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 691973	A1	19960117	EP 1994-912514	19940322
	R: BE, CH, DE, FR, GB, IT, LI, NL				
	JP 08508275	T2	19960903	JP 1994-521640	19940322
PRAI	GB 1993-6460		19930329		
	WO 1994-EP917		19940322		

OS MARPAT 122:31572
GI



I



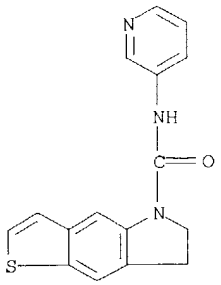
II

AB Thienoindole derivs. I [P = (un)substituted isoquinolinyl, quinolinyl, etc.; R2-R4 = H, alkyl, etc.; R5, R6 = H, alkyl; n = integer] were disclosed as as 5-HT2c and 5-HT2b antagonists. An example compound, 7,8-dihydro-6-(3-pyridinylcarbamoyl)thieno[3,2-e]indole (II) was prepared

IT **159730-79-7P**, 6,7-Dihydro-5-(3-pyridinylcarbamoyl)thieno[2,3-f]indole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of thieno[2,3-f]indolecarboxamide 5-HT2c and 5-HT2b antagonist)

RN 159730-79-7 CAPLUS

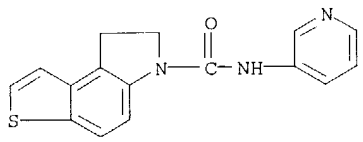
CN 5H-Thieno[2,3-f]indole-5-carboxamide, 6,7-dihydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



IT **159730-80-0P**, 7,8-Dihydro-6-(3-pyridinylcarbamoyl)thieno[3,2-e]indole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of thieno[3,2-e]indolecarboxamide 5-HT2c and 5-HT2b antagonist)

RN 159730-80-0 CAPLUS

CN 6H-Thieno[3,2-e]indole-6-carboxamide, 7,8-dihydro-N-3-pyridinyl- (9CI) (CA INDEX NAME)



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=> d his

     (FILE 'HOME' ENTERED AT 19:10:40 ON 17 SEP 2004)

     FILE 'REGISTRY' ENTERED AT 19:10:51 ON 17 SEP 2004
L1               STRUCTURE UPLOADED
L2             5 S L1
L3           248 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 19:12:06 ON 17 SEP 2004
L4           107 S L3
L5            62 S L4 AND SEROTONIN

     FILE 'REGISTRY' ENTERED AT 19:15:12 ON 17 SEP 2004
L6               STRUCTURE UPLOADED
L7             2 S L6  SUB=L3 SAMPLE
L8           118 S L6 SSS FULL SUB=L3

     FILE 'CAPLUS' ENTERED AT 19:16:46 ON 17 SEP 2004
L9            59 S L8
L10            2 S L7
L11           57 S L9 NOT L10
L12           57 S L11 NOT PYRROLOQUINOLIN?
L13           27 S L11 AND THU/RL
L14           13 S L13 AND PATENT/DT
L15           23 S L13 AND (SEROTONIN OR 5-HT)

=> s l13 and (depression or migraine or bulimia or sexual or sleep)
         70096 DEPRESSION
          4479 MIGRAINE
           822 BULIMIA
         28646 SEXUAL
         17143 SLEEP
L16            8 L13 AND (DEPRESSION OR MIGRAINE OR BULIMIA OR SEXUAL OR SLEEP)

=> s l16 not l14
L17            0 L16 NOT L14

=>
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=> d his

(FILE 'HOME' ENTERED AT 18:00:20 ON 17 SEP 2004)

FILE 'MEDLINE' ENTERED AT 18:00:34 ON 17 SEP 2004

L1	64	S	5HT2C
L2	911	S	5-HT2C
L3	953	S	L1 OR L2
L4	547	S	L3 AND ANTAGONIST?
L5	14	S	L4 AND REVIEW?

FILE 'STNGUIDE' ENTERED AT 18:03:51 ON 17 SEP 2004

FILE 'MEDLINE' ENTERED AT 18:05:02 ON 17 SEP 2004

L6	56	S	VOGEL CONFLICT
L7	3	S	L3 AND L6

=>

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=> d 1-14 bib abs

L5 ANSWER 1 OF 14 MEDLINE on STN
AN 2003602064 MEDLINE
DN PubMed ID: 14683466
TI Therapeutic potential of **5-HT2C** receptor **antagonists** in the treatment of anxiety disorders.
AU Wood Martyn D
CS Psychiatry Centre of Excellence for Drug Discovery, Department of Biology, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK.. martyn.wood-1@gsk.com
SO Current drug targets. CNS and neurological disorders, (2003 Dec) 2 (6) 383-7. Ref: 79
Journal code: 101151150. ISSN: 1568-007X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200401
ED Entered STN: 20031220
Last Updated on STN: 20040131
Entered Medline: 20040130
AB Anxiety disorders are the most common psychiatric illness affecting both adults and children. Following the observation that m-chlorophenylpiperazine(mCPP) induced anxiety-like states in patients and in animal models, it was shown that in man, mCPP behaves as a functionally selective agonist at the 5-hydroxytryptamine (5-HT)2C receptor. This caused much interest in the development of **antagonists** at the **5-HT2C** receptor for the treatment of anxiety disorders. This **review** examines the pre-clinical and clinical evidence for a role of the **5-HT2C** receptor in anxiety and evaluates the progress of compounds that target this therapeutic approach.

L5 ANSWER 2 OF 14 MEDLINE on STN
AN 2003439467 MEDLINE
DN PubMed ID: 14501253
TI Discriminative stimulus properties of antidepressant agents: a **review.**
AU Dekeyne A; Millan M J
CS Institut de Recherches Servier, Centre de Recherches de Croissy, Phychopharmacology Department, Croissy-sur-Seine, Paris, France.. anne.dekeyne@fr.netgrs.com
SO Behavioural pharmacology, (2003 Sep) 14 (5-6) 391-407. Ref: 150
Journal code: 9013016. ISSN: 0955-8810.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200401
ED Entered STN: 20030923
Last Updated on STN: 20040114
Entered Medline: 20040113
AB Though drug discrimination techniques have proven invaluable in characterizing the interoceptive properties of drugs of abuse, antipsychotics and anxiolytics, with the exception of some fragmentary data with tricyclic agents, surprisingly few studies have been undertaken with antidepressants. Nevertheless, the preferential dopamine (DA) reuptake inhibitor, bupropion, elicits a robust discriminative stimulus in rodents. Moreover, in rats trained on a two-lever FR-10 schedule for food reward, the selective serotonin (5-HT) reuptake inhibitor (SSRI), citalopram, and the noradrenaline (NA) reuptake inhibitor (NARI), reboxetine, elicit discriminative stimuli at doses that selectively elevate extracellular levels of 5-HT and NA, respectively. In generalization tests, mixed inhibitors of 5-HT and NA reuptake, such as venlafaxine, substitute for both citalopram and reboxetine, while SSRIs substitute for citalopram but not for reboxetine. Intriguingly, selective NARIs appear to substitute both for reboxetine and for citalopram though, owing to long-term instability of the citalopram cue, the latter observation will require confirmation. Bupropion and the atypical antidepressant, mirtazapine - a 5-HT2/alpha2-adrenoceptor (AR) **antagonist** devoid of affinity for 5-HT and NA reuptake sites - substitute for neither citalopram nor reboxetine, indicating that 'antidepressant' effects per se do not account for their interoceptive properties. Moreover, mirtazapine abolishes the citalopram cue, an action

mimicked by the selective **5-HT2C antagonist**, SB242,084. The discriminative stimulus elicited by reboxetine is blocked by the alpha1-AR **antagonist**, prazosin. In contrast, it is not significantly attenuated by the alpha2-AR **antagonist**, RX821,002, nor by betaxolol or ICI118,551, **antagonists** at alpha1- and alpha2-ARs, respectively. These observations indicate that 5-**HT2C** receptors and alpha1-ARs contribute to the discriminative stimulus properties of SSRIs and NARIs, respectively. The present article **reviews** the literature devoted to the discriminative stimulus properties of antidepressant agents as training drugs, focusing in particular upon novel data with citalopram and reboxetine. In addition, several open questions and future research directions are evoked. It would be of considerable interest to extend such drug discrimination studies to other classes of antidepressants or potential antidepressants, including venlafaxine, mirtazapine and **antagonists** at neuropeptide (corticotropin releasing factor1 and neurokinin1) receptors.

L5 ANSWER 3 OF 14 MEDLINE on STN
AN 2003162048 MEDLINE
DN PubMed ID: 12678838
TI **5-HT2C** receptor agonists as potential drugs for the treatment of obesity.
AU Bickerdike Michael J
CS Department of Molecular Pharmacology, Vernalis Research Ltd., Oakdene Court, 613 Reading Road. Winnersh, Wokingham, RG41 5UA, UK.. M.Bickerdike@vernalis.com
SO Current topics in medicinal chemistry, (2003) 3 (8) 885-97. Ref: 113
Journal code: 101119673. ISSN: 1568-0266.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 20030408
Last Updated on STN: 20030515
Entered Medline: 20030514
AB An association between the brain serotonin (5-HT) system and feeding has been postulated since the 1970's but it has only been in recent years that the nature of 5-HT-mediated hypophagia has become well understood, and the receptor subtypes responsible for the effect better defined. The invention and utilisation of subtype-selective 5-HT receptor **antagonists** has demonstrated that the 5-HT(2C) receptor is of paramount importance in this regard. Importantly, ethological studies of animal behaviour have shown that the hypophagia resulting from 5-HT(2C) receptor activation is likely to be a consequence of increased satiety and this is in contrast to hypophagia following 5-HT(2C) receptor activation. Furthermore, recent studies have also shown that 5-HT(2C) receptor agonists not only reduce feeding when acutely administered to rats or mice, they can also reduce body weight without inducing tolerance when administered chronically to obese animals. These observations have led researchers to conclude that selective 5-HT(2C) receptor agonists have the potential to be effective anti-obesity agents. Encouragingly, this suggestion is supported by both direct and indirect evidence from clinical studies. Indirect evidence stems from recent observations that the clinically effective anorectic agent d-fenfluramine exerts its hypophagic and weight-loss effects via 5-HT(2C) receptor activation. More direct clinical evidence derives from the use of the prototypical 5-HT(2C) receptor agonist m-chlorophenylpiperazine (mCPP), with which both acute hypophagia and body-weight loss have been observed. The current paper therefore **reviews** both the pre-clinical and clinical evidence supporting the use of 5-HT(2C) receptor agonists for the treatment of obesity and assesses the developments that have been made in this regard to date.

L5 ANSWER 4 OF 14 MEDLINE on STN
AN 2003137366 MEDLINE
DN PubMed ID: 12650852
TI 5-HT2A and **5-HT2C** receptors and their atypical regulation properties.
AU Van Oekelen Dirk; Luyten Walter H M L; Leysen Josee E
CS Johnson and Johnson Pharmaceutical, p/a Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium.
SO Life sciences, (2003 Apr 18) 72 (22) 2429-49. Ref: 163
Journal code: 0375521. ISSN: 0024-3205.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)

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General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 20030325
Last Updated on STN: 20030503
Entered Medline: 20030502
AB The 5-HT(2A) and 5-HT(2C) receptors belong to the G-protein-coupled receptor (GPCR) superfamily. GPCRs transduce extracellular signals to the interior of cells through their interaction with G-proteins. The 5-HT(2A) and 5-HT(2C) receptors mediate effects of a large variety of compounds affecting depression, schizophrenia, anxiety, hallucinations, dysthymia, sleep patterns, feeding behaviour and neuro-endocrine functions. Binding of such compounds to either 5-HT(2) receptor subtype induces processes that regulate receptor sensitivity. In contrast to most other receptors, chronic blockade of 5-HT(2A) and 5-HT(2C) receptors leads not to an up- but to a (paradoxical) down-regulation. This **review** deals with published data involving such non-classical regulation of 5-HT(2A) and 5-HT(2C) receptors obtained from in vivo and in vitro studies. The underlying regulatory processes of the agonist-induced regulation of 5-HT(2A) and 5-HT(2C) receptors, commonly thought to be desensitisation and resensitisation, are discussed. The atypical down-regulation of both 5-HT(2) receptor subtypes by antidepressants, antipsychotics and 5-HT(2) **antagonists** is **reviewed.** The possible mechanisms of this paradoxical down-regulation are discussed, and a new hypothesis on possible heterologous regulation of 5-HT(2A) receptors is proposed.

L5 ANSWER 5 OF 14 MEDLINE on STN
AN 2002663022 MEDLINE
DN PubMed ID: 12422559
TI [Mechanism of action of antidepressants and therapeutic perspectives]. Mecanisme d'action des antidepresseurs et perspectives therapeutiques.
AU Bourin M; David D J P; Jolliet P; Gardier A
CS Laboratoire de Neuropharmacologie Upres EAD MENRT, Institut de signalisation et d'innovation therapeutique (IFR75), Faculte de Pharmacie, Universite Paris-Sud, Chatenay-Malabry, France.. mbourin@sante.univ-nantes.fr
SO Therapie, (2002 Jul-Aug) 57 (4) 385-96. Ref: 51
Journal code: 0420544. ISSN: 0040-5957.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals
EM 200212
ED Entered STN: 20021109
Last Updated on STN: 20021217
Entered Medline: 20021210
AB Depression is an incapacitating disease which needs appropriate treatment. This article **reviews** the pharmacology of antidepressant drugs and the future perspectives of treating mood disorders such as depression. The foremost theory for explaining the biological basis of depression has been the monoamine hypothesis. Depression is due to a deficiency in one or other biogenic monoamines (serotonin, 5-HT; noradrenaline, NA; dopamine, DA). Antidepressant drugs are therefore classified according to their ability to improve monoaminergic transmission. Since this first theory, other explanations based on abnormal function of monoamine receptors or associated with impaired signalling pathways have been suggested. Notable progress has been accomplished in the treatment of major depressive disorders with new compounds recently discovered (selective serotonin reuptake inhibitors: SSRI; serotonin noradrenaline reuptake inhibitors: SNRI). Behavioural, electrophysiological and microdialysis studies have shown that serotonin (5-HT) receptors, mainly 5-HT1A, 5-HT1B and **5-HT2C** sub-types, exert a key role in modulating antidepressant activity. Indirect activation of neurotransmitter receptors by antidepressants may also lead, via increases in endogenous levels of serotonin in synapses in specific brain regions, to activation of various G proteins coupled to a receptor, signal of transduction, transcription factors and neurotrophic factors such as brain-derived neurotrophic factor (BDNF). Thus, depression may be considered as a transduction mechanism anomaly. This hypothesis needs to be clarified by molecular biology. Although antidepressants have improved the therapeutic potential compared to tricyclics (TCA) in terms of reduced side effects, a number of problems still occur with these drugs. Clinical effects are not always observed until after this time has elapsed (4-6 weeks) and a substantial proportion of depressed patients show only

partial or no response to antidepressants. Knowledge of the existence of links between neurotransmitter systems and the discovery of the most specific target, 5-HT receptors, should lead to improvements in antidepressant therapy. Developing drugs using innovative mechanisms such as directly acting on 5-HT receptors (5-HT1A agonists or 5-HT2 **antagonists**), would appear to be useful in the treatment of depression. The use of antidepressants in anxiety disorders such as obsessional compulsive disorders and even generalised anxiety, highlights the distinction between antidepressants and classic anxiolytics such as benzodiazepines, or even buspirone.

L5 ANSWER 6 OF 14 MEDLINE on STN
AN 2002157581 MEDLINE
DN PubMed ID: 11888564
TI Role of serotonin(2C) receptors in the control of brain dopaminergic function.
AU Di Matteo Vincenzo; Cacchio Marisa; Di Giulio Camillo; Esposito Ennio
CS Istituto di Ricerche Farmacologiche Mario Negri, Consorzio Mario Negri Sud, 66030 Santa Maria Imbaro, Chieti, Italy.
SO Pharmacology, biochemistry, and behavior, (2002 Apr) 71 (4) 727-34. Ref: 48
Journal code: 0367050. ISSN: 0091-3057.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200209
ED Entered STN: 20020313
Last Updated on STN: 20020912
Entered Medline: 20020911
AB There is substantial evidence that the functional status of mesocorticolimbic dopaminergic (DA) system originating in the ventral tegmental area (VTA) is under a phasic and tonic inhibitory control by the serotonergic system, which acts by stimulating serotonin(2C) (5-HT(2C)) receptor subtypes. This assertion is based upon a number of electrophysiological and biochemical data showing that 5-HT(2C) receptor agonists decrease, while 5-HT(2C) receptor **antagonists** enhance mesocorticolimbic DA function. On the other hand, it does not seem that 5-HT(2C) receptors play a relevant role in the control of nigrostriatal DA system originating in the substantia nigra pars compacta (SNc). The authors of this article **review** the most relevant data regarding the role of 5-HT(2C) receptors in the control of brain DA function and underline the importance of this subject in the search of new therapies for neuropsychiatric disorders such as depression, schizophrenia, drug addiction, and Parkinson's disease.

L5 ANSWER 7 OF 14 MEDLINE on STN
AN 2001435747 MEDLINE
DN PubMed ID: 11339973
TI Role of 5-HT(2C) receptors in the control of central dopamine function.
AU Di Matteo V; De Blasi A; Di Giulio C; Esposito E
CS Laboratory of Neurophysiology, Istituto di Ricerche Farmacologiche Mario Negri, Consorzio Mario Negri Sud, 66030 Santa Maria Imbaro (Chieti), Italy.
SO Trends in pharmacological sciences, (2001 May) 22 (5) 229-32. Ref: 34
Journal code: 7906158. ISSN: 0165-6147.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802
AB Substantial evidence suggests that the functional status of the mesocorticolimbic dopamine (DA) system originating in the ventral tegmental area is under a phasic and tonic inhibitory control by the 5-HT system that acts by stimulating 5-HT(2C) receptor subtypes. Indeed, electrophysiological and biochemical data demonstrate that 5-HT(2C) receptor agonists decrease, whereas 5-HT(2C) receptor **antagonists** enhance, mesocorticolimbic DA function. However, 5-HT(2C) receptors do not appear to play a relevant role in the control of the nigrostriatal DA system originating in the substantia nigra pars compacta. In this article, the role of 5-HT(2C) receptors in the control of brain DA

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function will be **reviewed**, and the search for new therapies for neuropsychiatric disorders, such as depression, schizophrenia and drug addiction, based on these findings will be discussed.

L5 ANSWER 8 OF 14 MEDLINE on STN
AN 2001021906 MEDLINE
DN PubMed ID: 10991983
TI Inverse agonist activity of atypical antipsychotic drugs at human 5-hydroxytryptamine2C receptors.
AU Herrick-Davis K; Grinde E; Teitler M
CS Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, New York, USA.. daviskh@mail.amc.edu
NC MH-56650 (NIMH)
MH-57019 (NIMH)
SO Journal of pharmacology and experimental therapeutics, (2000 Oct) 295 (1) 226-32.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001103
AB Clozapine is the prototype atypical antipsychotic drug, producing little or no extrapyramidal side effects, while improving negative symptoms of psychosis. Clozapine's high affinity for serotonin receptors has been hypothesized to confer the unique antipsychotic properties of this drug. Recently, we demonstrated that both typical and atypical antipsychotic drugs are inverse agonists at constitutively active 5-hydroxytryptamine2A (5-HT(2A)) receptors. To determine whether inverse agonist activity at 5-HT(2C) receptors plays a role in antipsychotic efficacy, typical and atypical antipsychotic drugs were tested for inhibition of basal inositol phosphate production in mammalian cells expressing rat or human 5-HT(2C) receptors. Atypical antipsychotic drugs (sertindole, clozapine, olanzapine, ziprasidone, risperidone, zotepine, tiospirone, fluperlapine, tenilapine) displayed potent inverse agonist activity at rat and human 5-HT(2C) receptors. Typical antipsychotic drugs (chlorpromazine, loxapine, thioridazine, prochlorperazine, perphenazine, mesoridazine, trifluperidol, fluphenazine, spiperone, haloperidol, pimozide, penfluridol, thiothixene) were devoid of inverse agonist activity, with the exception of loxapine. We **review** the evidence that loxapine has unique properties characteristic of both atypical and typical antipsychotic drugs. Several typical antipsychotic drugs (chlorpromazine, thioridazine, spiperone, thiothixene) displayed neutral **antagonist** activity by reversing clozapine inverse agonism. These data suggest that 5-HT(2C) inverse agonist activity is associated with atypical antipsychotic drugs with moderate to high affinity for 5-HT(2C) receptors, and imply that effects of atypical antipsychotic drugs on the 5-HT(2C) receptor may play a role in their unique clinical properties. These data also imply that dysfunction of brain 5-HT(2C) receptor systems may be one of the factors involved in the etiology of psychosis.

L5 ANSWER 9 OF 14 MEDLINE on STN
AN 97203757 MEDLINE
DN PubMed ID: 9051329
TI Headache induced by serotonergic agonists--a key to the interpretation of migraine pathogenesis?.
AU Panconesi A; Sicuteri R
CS Institute of Internal Medicine IV, University of Florence, Italy.
SO Cephalalgia : an international journal of headache, (1997 Feb) 17 (1) 3-14. Ref: 147
Journal code: 8200710. ISSN: 0333-1024.
CY Norway
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199704
ED Entered STN: 19970507
Last Updated on STN: 19970507
Entered Medline: 19970429
AB Serotonergic agonists such as m-chlorophenylpiperazine (m-CPP) and fenfluramine may induce migraine attacks. This has led to opposing theories concerning the role of 5-hydroxytryptamine (5HT) in triggering migraine attacks; is there hyperfunction or hypofunction of the central

serotonergic system. Our **review** of the literature strongly suggests that m-CPP and fenfluramine provoke migraine attacks by stimulating, directly or indirectly, the **5HT2C**/5HT2B receptors, although there is no total agreement with this interpretation. Central 5HT hypersensitivity in migraine patients, probably due to 5HT neuronal depletion, is proposed on the basis of **review** of electrophysiological tests and neuroendocrine challenge paradigms.

L5 ANSWER 10 OF 14 MEDLINE on STN
AN 96380480 MEDLINE
DN PubMed ID: 8788493
TI Novel discriminatory ligands for 5-HT2B receptors.
AU Baxter G S
CS Neurology Research Department, SmithKline Beecham Pharmaceuticals, Essex, UK.
SO Behavioural brain research, (1996) 73 (1-2) 149-52. Ref: 19
Journal code: 8004872. ISSN: 0166-4328.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961204
AB The 5-HT2B receptor is the most recent addition to the 5-HT2 receptor family and shares strong operational similarities with the structurally related 5-HT2A and **5-HT2C** receptor subtypes. The strength of the pharmacological association, particularly between 5-HT2B and **5-HT2C** receptors, suggests a need to consider carefully the use of ligands which may now be regarded as somewhat non-selective for the receptors in this class. The possibility that biological activity previously supposed to involve **5-HT2C** receptors may actually involve 5-HT2B receptors highlights a need to develop ligands with improved selectivity profiles. In this regard, medicinal chemistry continues to provide novel ligands which, if truly selective, should facilitate our understanding of the physiology, pathophysiology and therapeutic potential of 5-HT2B receptor modulation. This article **reviews** some of the newest ligands which may be used in the discrimination and characterisation of 5-HT2B receptor function.

L5 ANSWER 11 OF 14 MEDLINE on STN
AN 96380463 MEDLINE
DN PubMed ID: 8788476
TI Serotonergic regulation of associative learning.
AU Harvey J A
CS Department of Pharmacology, Medical College of Pennsylvania and Hahnemann University, Philadelphia 19129, USA.. harvey@ccc.medcolpa.edu
NC MH16841-26 (NIMH)
SO Behavioural brain research, (1996) 73 (1-2) 47-50. Ref: 22
Journal code: 8004872. ISSN: 0166-4328.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961204
AB This paper presents a **review** of studies dealing with the effects of 5-HT agonists and **antagonists** on learning as measured by classical conditioning of the rabbit's nictitating membrane response or the conditioned avoidance response in the rat. These studies indicate that the 5-HT2A/2C receptors are importantly involved in learning. In these behavioral paradigms, enhancement of learning is only produced by drugs that are agonists at the 5-HT2A/2C receptors, and this enhancement is only blocked by drugs that are **antagonists** at these receptors. In addition, evidence is presented for the existence of two classes of 5-HT2A/2C **antagonists** consisting of negative **antagonists** that retard learning when given alone (ritanserin, MDL-11,939, pizotifen and cyproheptadine) and those that are neutral **antagonists** in that they have no effect on learning (ketanserin, mianserin, BOL and LY-53,857). However, both the neutral and negative

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antagonists are equally capable of blocking the enhancement of learning produced by 5-HT2A/2C agonists. It was concluded that 5-HT2A and/or **5-HT2C** agonists may provide a new approach to the treatment of learning disorders in aging or Alzheimer's disease.

L5 ANSWER 12 OF 14 MEDLINE on STN
AN 96063343 MEDLINE
DN PubMed ID: 7583621
TI Role of serotonin in the action of atypical antipsychotic drugs.
AU Meltzer H Y
CS Department of Psychiatry, University Hospitals of Cleveland, OH 44106-5078, USA.
NC MH 41684 (NIMH)
MH 47808 (NIMH)
MO1RR00080 (NCRR)
SO Clinical neuroscience (New York, N.Y.), (1995) 3 (2) 64-75. Ref: 162
Journal code: 9315128. ISSN: 1065-6766.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199511
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951129
AB Clozapine is the first of a new generation of antipsychotic drugs which constitutes a major advance in the treatment of schizophrenia. Numerous theories have been proposed to explain the advantages of clozapine over typical neuroleptics. Most of these focus on its effects on dopaminergic and serotonergic neurotransmission. This article **reviews** the effects of clozapine and related antipsychotic drugs on dopamine (DA) D1, D2, and D4, and serotonin (5-HT) 5-HT2A, **5-HT2C**, 5-HT3, 5-HT6, and 5-HT7 receptors, as well as its ability to modulate DA and 5-HT release. Clozapine and other atypical antipsychotic drugs share the ability to cause fewer extrapyramidal symptoms at clinically effective doses. This may be related to their potent 5-HT2A and weak D2 receptor blocking properties, a profile shared by risperidone, melperone, olanzapine, amperozide, HP-873, seroquel, sertindole, and ziprasidone. The basis for the superior ability of clozapine to treat negative symptoms and enhance cognitive function compared to typical neuroleptic drugs in schizophrenic patients has not yet been ascertained, but there is evidence that its effect on 5-HT2A, D2, or D4 receptors may be important. Other aspects of the pharmacology of clozapine which may contribute to its actions include potent alpha 1-adrenergic, M1, M2, M3, and M5 receptor blocking properties, as well as M4 agonist effects.

L5 ANSWER 13 OF 14 MEDLINE on STN
AN 95306478 MEDLINE
DN PubMed ID: 7786883
TI Phosphoinositide system-linked serotonin receptor subtypes and their pharmacological properties and clinical correlates.
AU Pandey S C; Davis J M; Pandey G N
CS Department of Psychiatry, College of Medicine, University of Illinois at Chicago 60612, USA.
SO Journal of psychiatry & neuroscience : JPN, (1995 May) 20 (3) 215-25.
Ref: 128
Journal code: 9107859. ISSN: 1180-4882.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950807
Last Updated on STN: 19970203
Entered Medline: 19950727
AB Serotonergic neurotransmission represents a complex mechanism involving pre- and post-synaptic events and distinct 5-HT receptor subtypes. Serotonin (5-HT) receptors have been classified into several categories, and they are termed as 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7 type receptors. 5-HT1 receptors have been further subdivided into 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E and 5-HT1F. 5-HT2 receptors have been divided into 5-HT2A, 5-HT2B and **5-HT2C** receptors. All 5-HT2 receptor subtypes are linked to the multifunctional phosphoinositide (PI) signalling system. 5-HT3 receptors are considered ion-gated receptors and

are also linked to the PI signalling system by an unknown mechanism. The 5-HT2A receptor subtype is the most widely studied of the 5-HT receptors in psychiatric disorders (for example, suicide, depression and schizophrenia) as well as in relation to the mechanism of action of antidepressant drugs. The roles of **5-HT2C** and 5-HT3 receptors in psychiatric disorders are less clear. These 5-HT receptors also play an important role in alcoholism. It has been shown that 5-HT2A, **5-HT2C** and 5-HT3 **antagonists** cause attenuation of alcohol intake in animals and humans. However, the exact mechanisms are unknown. The recent cloning of the cDNAs for 5-HT2A, **5-HT2C** and 5-HT3 receptors provides the opportunity to explore the molecular mechanisms responsible for the alterations in these receptors during illness as well as pharmacotherapy. This **review** article will focus on the current research into the pharmacological properties, molecular biology, and clinical correlates of 5-HT2A, **5-HT2C** and 5-HT3 receptors.

L5 ANSWER 14 OF 14 MEDLINE on STN
AN 95288008 MEDLINE
DN PubMed ID: 7770190
TI Dopamine receptor supersensitivity.
AU Kostrzewa R M
CS Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City 37614, USA.
NC NS 29505 (NINDS)
SO Neuroscience and biobehavioral reviews, (1995 Spring) 19 (1) 1-17. Ref: 119
Journal code: 7806090. ISSN: 0149-7634.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950713
Last Updated on STN: 19950713
Entered Medline: 19950706
AB Dopamine (DA) receptor supersensitivity refers to the phenomenon of an enhanced physiological, behavioral or biochemical response to a DA agonist. Literature related to ontogenetic aspects of this process was **reviewed.** Neonatal 6-hydroxydopamine (6-OHDA) destruction of rat brain DA neurons produces overt sensitization to D1 agonist-induced oral activity, overt sensitization of some D2 agonist-induced stereotyped behaviors and latent sensitization of D1 agonist-induced locomotor and some stereotyped behaviors. This last process is unmasked by repeated treatments with D1 (homologous "priming") or D2 (heterologous "priming") agonists. A serotonin (5-HT) neurotoxin (5,7-dihydroxytryptamine) and **5-HT2C** receptor **antagonist** (mianserin) attenuate some enhanced behavioral effects of D1 agonists, indicating that 5-HT neurochemical systems influence D1 receptor sensitization. Unlike the relative absence of change in brain D1 receptor number, DA D2 receptor proliferation accompanies D2 sensitization in neonatal 6-OHDA-lesioned rats. Robust D2 receptor supersensitization can also be induced in intact rats by repeated treatments in ontogeny with the D2 agonist quinpirole. In these rats quinpirole treatments produce vertical jumping at 3-5 wk after birth and subsequent enhanced quinpirole-induced antinociception and yawning. The latter is thought to represent D3 receptor sensitization. Except for enhanced D1 agonist-induced expression of c-fos, there are no changes in the receptor or receptor-mediated processes which account for receptor sensitization. Adaptive mechanisms by multiple "in series" neurons with different neurotransmitters may account for the phenomenon known as receptor supersensitivity.

10813347

=> d 1-3 bib abs

L7 ANSWER 1 OF 3 MEDLINE on STN
AN 2000490043 MEDLINE
DN PubMed ID: 11041316
TI The selective serotonin (5-HT)1A receptor ligand, S15535, displays anxiolytic-like effects in the social interaction and Vogel models and suppresses dialysate levels of 5-HT in the dorsal hippocampus of freely-moving rats. A comparison with other anxiolytic agents.
AU Dekeyne A; Brocco M; Adhumeau A; Gobert A; Millan M J
CS Institut de Recherches Servier, Centre de Recherches de Croissy, Psychopharmacology Department, Paris, France.
SO Psychopharmacology, (2000 Sep) 152 (1) 55-66.
Journal code: 7608025. ISSN: 0033-3158.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20030118
Entered Medline: 20010215
AB RATIONALE: The benzodioxane, S15535, possesses low intrinsic activity and marked selectivity at 5-HT1A receptors, hippocampal populations of which are implicated in anxious states. OBJECTIVE: Herein, we examined its potential anxiolytic actions in relation to its influence upon extracellular levels of 5-HT in the dorsal hippocampus of freely-moving rats. Its effects were compared with those of other anxiolytic agents: the 5-HT1A agonists, buspirone and 8-hydroxy-2-(di-n-propylamino)-tetralin HBr (8-OH-DPAT), the **5-HT2C** antagonist, SB206,553 and the benzodiazepine, diazepam. METHODS: Potential anxiolytic actions were evaluated in the **Vogel conflict** paradigm (increase in punished responses) and the social interaction (SI) test (increase in active SI) in rats. Extracellular levels of 5-HT were determined by microdialysis. RESULTS: In analogy to diazepam. S15535 increased punished responses in the Vogel test. This action was dose dependently expressed over a broad (16-fold) dose range. Buspirone and 8-OH-DPAT were likewise active, but yielded highly biphasic dose-response curves. SB206,553 was dose dependently active in this model. In the SI test, S15535 similarly mimicked the anxiolytic-like effect of diazepam and was active over a broad dose range. Buspirone and 8-OH-DPAT again showed biphasic dose-response curves, as did SB206,553. In both the Vogel and SI tests, the anxiolytic-like effects of S15535 were abolished by the selective 5-HT1A receptor antagonist, WAY100,635, which was inactive alone. S15535 exerted its anxiolytic-like effects with a more pronounced separation to motor-disruptive doses than the other drugs. Finally, S15535 suppressed dialysate levels of 5-HT in the dorsal hippocampus, an action abolished by WAY100,635. Buspirone, 8-OH-DPAT and diazepam, but not SB206,553, also reduced 5-HT levels. CONCLUSION: Likely reflecting its distinctive ability to selectively and preferentially activate pre- versus postsynaptic 5-HT1A receptors, S15535 suppresses hippocampal 5-HT release and displays marked anxiolytic-like effects over a broad dose range in the relative absence of motor perturbation.

L7 ANSWER 2 OF 3 MEDLINE on STN
AN 2000117725 MEDLINE
DN PubMed ID: 10650160
TI Effects of RO 60 0175, a 5-HT(2C) receptor agonist, in three animal models of anxiety.
AU Kennett G; Lightowler S; Trail B; Bright F; Bromidge S
CS Neurobehavioural Research, SmithKline Beecham Pharmaceuticals, New frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK.
SO European journal of pharmacology, (2000 Jan 10) 387 (2) 197-204.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000407
Last Updated on STN: 20000407
Entered Medline: 20000328
AB There is some controversy as to whether 5-HT(2C) receptor agonists are anxiogenic or anxiolytic. The effects of the novel 5-HT(2C) receptor agonist, (S)-2-chloro-5-fluoro-indol-1-yl)-1-methyl ethylamine fumarate (RO 60 0175), in three models of anxiety were therefore tested. RO 60 0175 was found to induce hypolocomotion in rats at doses greater than 0.5 mg/kg s.c., an effect reversed by the selective 5-HT(2C) receptor

antagonist, SB-242084. RO 60 0175 did not elicit anxiolytic-like responses in the social interaction test under high light unfamiliar conditions, but suppressed both time spent in social interaction and locomotion at doses of 1 and 3 mg/kg s.c., suggesting a sedative response. In the **Vogel conflict** test, RO 60 0175 had no significant action on the number of shocks taken. In the Geller-Seifter test, RO 60 0175 (0.3 and 1 mg/kg s.c.) simultaneously reduced both unpunished and punished lever pressing, a profile consistent with sedation. Finally, RO 60 0175 was tested in a rat social interaction test under low light familiar conditions optimal for the detection of anxiogenic-like responses. At 1 and 3 mg/kg s.c., RO 60 0175 reduced both time spent in social interaction and concurrent locomotion, a profile more consistent with sedation than anxiogenesis. In conclusion, RO 60 0175 induced sedative-like responses via 5-HT(2C) receptor activation, but was neither anxiolytic, nor clearly anxiogenic at the doses tested.

L7 ANSWER 3 OF 3 MEDLINE on STN
AN 1999101774 MEDLINE
DN PubMed ID: 9886683
TI Anxiolytic-like actions of BW 723C86 in the rat **Vogel conflict** test are 5-HT2B receptor mediated.
AU Kennett G A; Trail B; Bright F
CS Neurobehavioural Research, SmithKline Beecham Pharmaceuticals, Harlow, Essex, UK.
SO Neuropharmacology, (1998 Dec) 37 (12) 1603-10.
Journal code: 0236217. ISSN: 0028-3908.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990402
Last Updated on STN: 20030118
Entered Medline: 19990323
AB The 5-HT2B receptor agonist, BW 723C86 (10, 30(mg/kg i.p. 30 min pre-test), increased the number of punishments accepted in a rat Vogel drinking conflict paradigm over 3 min, as did the benzodiazepine anxiolytics, chlordiazepoxide (2.5-10 mg/kg p.o. 1 h pre-test) and alprazolam (0.2-5 mg/kg p.o. 1 h pre-test), but not the **5-HT2C**/2B receptor agonist, m-chlorophenylpiperazine (mCPP, 0.3-3 mg/kg i.p) or the 5-HT1A receptor agonist, buspirone (5-20 mg/kg p.o. 1 h pre-test). The effect of BW 723C86 was unlikely to be secondary to enhanced thirst, as BW 723C86 did not increase the time that rats with free access to water spent drinking, nor did it reduce sensitivity to shock in the apparatus. The anti-punishment effect of BW 723C86 was opposed by prior treatment with the 5-HT2/2B receptor antagonist, SB-206553 (10 and 20 mg/kg p.o. 1 h pre-test), and the selective 5-HT2B receptor antagonist, SB-215505 (1 and 3 mg/kg p.o. 1 h pre-test), but not by the selective **5-HT2C** receptor antagonist, SB-242084 (5 mg/kg p.o.), or the 5-HT1A receptor antagonist, WAY 100635 (0.1 or 0.3 mg/kg s.c. 30 min pre-test). Thus, the anti-punishment action of BW 723C86 is likely to be 5-HT2B receptor mediated. This is consistent with previous reports that BW 723C86 exhibited anxiolytic-like properties in both the social interaction and Geller-Seifter conflict tests.

10813347

=> d 1-16 bib abs

L22 ANSWER 1 OF 16 MEDLINE on STN
AN 2004227265 IN-PROCESS
DN PubMed ID: 15125929
TI Synthesis and **structure-activity** relationship of 2-(aminoalkyl)-3,3a,8,12b-tetrahydro-2H-dibenzocyclohepta[1,2-b]furan derivatives: a novel series of 5-HT(2A/2C) receptor antagonists.
AU Cid Jose; Alonso Jose M; Andres Jose I; Fernandez Javier; Gil Pilar; Iturrino Laura; Matesanz Encarna; Meert Theo F; Megens Anton; Sipido Victor K; Trabanco Andres A
CS Johnson & Johnson Pharmaceutical Research & Development, a division of Janssen-Cilag, Medicinal Chemistry Department, Jarama s/n, 45007 Toledo, Spain.. jcid@prdes.jnj.com
SO Bioorganic & medicinal chemistry letters, (2004 Jun 7) 14 (11) 2765-71. Journal code: 9107377. ISSN: 0960-894X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040506
Last Updated on STN: 20040602
AB Following the program started at Johnson & Johnson Pharmaceutical Research & Development searching for 5-HT(2A/2C) **antagonists** we now report on the synthesis of a series of substituted 2-(aminomethyl)-3,3a,8,12b-tetrahydro-2H-dibenzocyclohepta[1,2-b]furan derivatives. The 5-HT2A, **5-HT2C** and H1 receptor affinities of the described compounds are reported. The mCCP **antagonistic** activity of a set of selected molecules is also reported.

L22 ANSWER 2 OF 16 MEDLINE on STN
AN 2000121652 MEDLINE
DN PubMed ID: 10658582
TI Model studies on a synthetically facile series of N-substituted phenyl-N'-pyridin-3-yl ureas leading to 1-(3-pyridylcarbamoyl) indolines that are potent and selective 5-HT(2C/2B) receptor antagonists.
AU Bromidge S M; Dabbs S; Davies D T; Davies S; Duckworth D M; Forbes I T; Gadre A; Ham P; Jones G E; King F D; Saunders D V; Thewlis K M; Vyas D; Blackburn T P; Holland V; Kennett G A; Riley G J; Wood M D
CS SmithKline Beecham Pharmaceuticals Discovery Research, New Frontiers Science Park, Harlow, Essex, UK.. steve_bromidge-1@sbphrd.com
SO Bioorganic & medicinal chemistry, (1999 Dec) 7 (12) 2767-73. Journal code: 9413298. ISSN: 0968-0896.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323
AB A model series of **5-HT2C antagonists** have been prepared by rapid parallel synthesis. These N-substituted phenyl-N'-pyridin-3-yl ureas were found to have a range of **5-HT2C** receptor affinities and selectivities over the closely related 5-HT2A receptor. Extrapolation of simple SAR, derived from this set of compounds, to the more active but synthetically more complex 1-(3-pyridylcarbamoyl)indoline series allowed us to target optimal substitution patterns and identify potent and selective 5-HT(2C/2B) **antagonists.**

L22 ANSWER 3 OF 16 MEDLINE on STN
AN 1999274431 MEDLINE
DN PubMed ID: 10344634
TI Simple O-acylated derivatives of lysergol and dihydrolysergol-I: synthesis and interaction with 5-HT2A, 5-HT2C and 5-HT1B receptors, and alpha1 adrenergic receptors.
AU Pertz H H; Brown A M; Gager T L; Kaumann A J
CS Fachbereich Pharmazie, Freie Universitat Berlin, Germany.
SO Journal of pharmacy and pharmacology, (1999 Mar) 51 (3) 319-30. Journal code: 0376363. ISSN: 0022-3573.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990806
Last Updated on STN: 19990806

10813347

Entered Medline: 19990728

AB A series of simple O-acylated derivatives of the naturally occurring clavine alkaloids lysergol and dihydrolysergol-I were synthesized and tested in-vitro for their ability to interact with 5-HT2A receptors in rat tail artery, **5-HT2C** receptors in piglet choroid plexus, 5-HT1B receptors in guinea-pig iliac artery and alpha1-adrenergic receptors in rat aorta. In contrast to the classical ergoline 5-HT2A receptor **antagonists** methysergide and LY53857, the compounds produced competitive antagonism of the 5-HT response in rat tail artery. Affinities of ergolines 3-14 were higher (pA2 values of 7.33-8.40) than those of the parent alcohols lysergol (1) and dihydrolysergol-I (2), respectively. The introduction of an isopropyl substituent at the N(1) position of the compounds failed to enhance 5-HT2A receptor affinity. Compounds 3-14 exhibited lower affinities for alpha1-adrenergic receptors than for 5-HT2A receptors. In particular, those lysergol derivatives that had an isopropyl substituent at the N(1) position were highly specific 5-HT2A receptor **antagonists** (ratio 5-HT2A/alpha1 = 302-3548). Selected derivatives of lysergol (3-5, 9-11) which were assayed for radioligand binding at **5-HT2C** receptors in piglet choroid plexus had affinities that were similar to those found in rat tail artery. Additionally, lysergol and its N(1)-unsubstituted derivatives were found to be partial agonists (alpha of 0.2-0.4) for **5-HT2C** receptor-mediated inositol phosphate accumulation in piglet choroid plexus. On the other hand, analogues with an isopropyl substituent at N(1) showed no measurable agonist activity. The observation that N(1)-unsubstituted derivatives of lysergol possessed agonist properties at **5-HT2C** receptors whereas their agonist activity at 5-HT2A receptors was marginal (alpha of 0.05 for compound 3 at 1 microM) or not measurable, suggests that these compounds have different abilities to cause conformational change at the two receptor types. Selected derivatives of lysergol (3-5, 9-11) which were examined as ligands for 5-HT1B receptors in guinea-pig iliac artery caused insurmountable blockade of the contractile effect of 5-HT. N(1)-isopropyl derivatives had 30-50-fold lower affinities for 5-HT1B receptors of this tissue than their N(1)-unsubstituted analogues. It is concluded that O-acylated derivatives of the clavine alkaloids lysergol and dihydrolysergol-I mimic therapeutically relevant ergolines due to the complexity of their pharmacological profile as partial agonists and **antagonists** at 5-HT2A, **5-HT2C** and 5-HT1B receptors, and at alpha1-adrenergic receptors.

L22 ANSWER 4 OF 16 MEDLINE on STN
AN 1999129922 MEDLINE
DN PubMed ID: 9933142
TI Comparisons of hallucinogenic phenylisopropylamine binding affinities at cloned human 5-HT2A, -HT(2B) and 5-HT2C receptors.
AU Nelson D L; Lucaites V L; Wainscott D B; Glennon R A
CS Neuroscience Research, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, USA.
NC DA 01642 (NIDA)
SO Naunyn-Schmiedeberg's archives of pharmacology, (1999 Jan) 359 (1) 1-6. Journal code: 0326264. ISSN: 0028-1298.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990601

AB Since the classical hallucinogens were initially reported to produce their behavioral effects via a 5-HT2 agonist mechanism (i.e., the 5-HT2 hypothesis of hallucinogen action), 5-HT2 receptors have been demonstrated to represent a family of receptors that consists of three distinct subpopulations: 5-HT2A, 5-HT2B, and **5-HT2C** receptors. Today, there is greater support for 5-HT2A than for **5-HT2C** receptor involvement in the behavioral effects evoked by these agents. However, with the recent discovery of 5-HT2B receptors, a new question arises: do classical hallucinogens bind at 5-HT2B receptors? In the present study we examined and compared the binding of 17 phenylisopropylamines at human 5-HT2A, 5-HT2B, and **5-HT2C** receptors. Although there was a notable positive correlation ($r>0.9$) between the affinities of the agents at all three populations of 5-HT2 receptors, structural modification resulted only in small differences in 5-HT2B receptor affinity such that the range of affinities was only about 50-fold. As with 5-HT2A and **5-HT2C** receptor affinity, there is a significant correlation ($r>0.9$, $n=8$) between 5-HT2B receptor affinity and human hallucinogenic potency. Nevertheless,

given that 5-HT2A and 5-HT2A/2C **antagonists** - **antagonists** with low affinity for 5-HT2B receptors - have been previously shown to block the stimulus effects of phenylisopropylamine hallucinogens, it is likely that 5-HT2A receptors play a more prominent role than 5-HT2B and **5-HT2C** receptors in mediating such effects despite the affinity of these agents for all three 5-HT2 receptor subpopulations.

L22 ANSWER 5 OF 16 MEDLINE on STN
AN 1999055320 MEDLINE
DN PubMed ID: 9836624
TI Spiperone: influence of spiro ring substituents on 5-HT2A serotonin receptor binding.
AU Metwally K A; Dukat M; Egan C T; Smith C; DuPre A; Gauthier C B; Herrick-Davis K; Teitler M; Glennon R A
CS Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, Virginia 23298-0540, USA.
NC DA-01642 (NIDA)
SO Journal of medicinal chemistry, (1998 Dec 3) 41 (25) 5084-93.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199901
ED Entered STN: 19990115
Last Updated on STN: 20030118
Entered Medline: 19990107
AB Spiperone (1) is a widely used pharmacological tool that acts as a potent dopamine D2, serotonin 5-HT1A, and serotonin 5-HT2A **antagonist.** Although spiperone also binds at **5-HT2C** receptors, it is one of the very few agents that display some (ca. 1000-fold) binding selectivity for 5-HT2A versus **5-HT2C** receptors and, hence, might serve as a useful template for the development of novel 5-HT2A **antagonists** if the impact of its various substituent groups on binding was known. In the present investigation we focused on the 1, 3,8-triazaspiro[4.5]decanone portion of spiperone and found that replacement of the N1-phenyl group with a methyl group only slightly decreased affinity for cloned rat 5-HT2A receptors. However, N1-methyl derivatives displayed significantly reduced affinity for 5-HT1A, **5-HT2C**, and dopamine D2 receptors. Several representative examples were shown to behave as 5-HT2 **antagonists.** As such, N1-alkyl analogues of spiperone may afford entry into a novel series of 5-HT2A-selective **antagonists.**

L22 ANSWER 6 OF 16 MEDLINE on STN
AN 1998285679 MEDLINE
DN PubMed ID: 9622555
TI Substituted naphthofurans as hallucinogenic phenethylamine-ergoline hybrid molecules with unexpected muscarinic antagonist activity.
AU Monte A P; Marona-Lewicka D; Lewis M M; Mailman R B; Wainscott D B; Nelson D L; Nichols D E
CS Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy, Purdue University, West Lafayette, Indiana 47907, USA.
NC DA02189 (NIDA)
HD03310 (NICHD)
MH33127 (NIMH)
+
SO Journal of medicinal chemistry, (1998 Jun 4) 41 (12) 2134-45.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980708
Last Updated on STN: 19980708
Entered Medline: 19980624
AB A series of substituted racemic naphthofurans were synthesized as "hybrid" molecules of the two major prototypical hallucinogenic drug classes, the phenethylamines and the tryptamines/ergolines. Although it was hypothesized that these new agents might possess high affinity for the serotonin 5-HT2A/2C receptor subtypes, unexpected affinity for muscarinic receptors was observed. The compounds initially synthesized for this study were (+/-)-anti- and syn-4-amino-6-methoxy-2a,3,4,5-tetrahydro-2H-naphtho[1,8-bc]furan (4a,b), respectively, and their 8-bromo derivatives 4c,d, respectively. The brominated primary amines 4c,d were assayed initially for activity in the two-lever drug discrimination (DD) paradigm

in rats trained to discriminate saline from LSD tartrate (0. 08 mg/kg). Also, 4c,d were evaluated for their ability to compete against agonist and **antagonist** radioligands at cloned human 5-HT2A, 5-HT2B, and **5-HT2C** receptors. After the syn diastereomers were found to have the highest activity in these preliminary assays, the N-alkylated analogues syn-N,N-dimethyl-4-amino-6-methoxy-2a,3,4, 5-tetrahydro-2H-naphtho[1,8-bc]furan (4e) and syn-N, N-dipropyl-4-amino-6-methoxy-2a,3,4,5-tetrahydro-2H-naphtho[1, 8-bc]furan (4f) were prepared and assayed for their affinities at [3H]ketanserin-labeled 5-HT2A and [3H]-8-OH-DPAT-labeled 5-HT1A sites. All of the molecules tested had relatively low affinity for serotonin receptors, yet a preliminary screen indicated that compound 4d had affinity for muscarinic receptors. Thus, 4b,d,e were evaluated for their affinity at muscarinic M1-M5 receptors and also assessed for their functional characteristics at the M1 and M2 isoforms. Compound 4d had affinities of 12-33 nM at all of the muscarinic sites, with 4b,e having much lower affinity. All three compounds fully antagonized the effects of carbachol at the M1 receptor, while only 4d completely antagonized carbachol at the M2 receptor. The fact that the naphthofurans lack LSD-like activity suggests that they do not bind to the serotonin receptor in a way such that the tricyclic naphthofuran nucleus is bioisosteric with, and directly superimposable upon, the A, B, and C rings of LSD. This also implies, therefore, that the hallucinogenic phenethylamines cannot be directly superimposed on LSD in a common binding orientation for these two chemical classes, contrary to previous hypotheses.

L22 ANSWER 7 OF 16 MEDLINE on STN
AN 1998241652 MEDLINE
DN PubMed ID: 9572885
TI Novel and selective **5-HT2C**/2B receptor **antagonists** as potential anxiolytic agents: synthesis, quantitative **structure-activity** relationships, and molecular modeling of substituted 1-(3-pyridylcarbamoyl)indolines.
AU Bromidge S M; Dabbs S; Davies D T; Duckworth D M; Forbes I T; Ham P; Jones G E; King F D; Saunders D V; Starr S; Thewlis K M; Wyman P A; Blaney F E; Naylor C B; Bailey F; Blackburn T P; Holland V; Kennett G A; Riley G J; Wood M D
CS SmithKline Beecham Pharmaceuticals, Discovery Research, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, England.
SO Journal of medicinal chemistry, (1998 May 7) 41 (10) 1598-612.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199805
ED Entered STN: 19980609
Last Updated on STN: 19990129
Entered Medline: 19980528
AB The synthesis, biological activity, and molecular modeling of a novel series of substituted 1-(3-pyridylcarbamoyl)indolines are reported. These compounds are isosteres of the previously published indole urea 1 (SB-206553) and illustrate the use of aromatic disubstitution as a replacement for fused five-membered rings in the context of **5-HT2C**/2B receptor **antagonists.** By targeting a region of space previously identified as sterically allowed at the **5-HT2C** receptor but disallowed at the 5-HT2A receptor, we have identified a number of compounds which are the most potent and selective **5-HT2C**/2B receptor **antagonists** yet reported. 46 (SB-221284) was selected on the basis of its overall biological profile for further evaluation as a novel, potential nonsedating anxiolytic agent. A CoMFA analysis of these compounds produced a model with good predictive value and in addition good qualitative agreement with both our **5-HT2C** receptor model and our proposed binding mode for this class of ligands within that model.

L22 ANSWER 8 OF 16 MEDLINE on STN
AN 1998120635 MEDLINE
DN PubMed ID: 9459014
TI O-methylasparvenone, a nitrogen-free serotonin antagonist.
AU Bos M; Canesso R; Inoue-Ohga N; Nakano A; Takehana Y; Sleight A J
CS Pharma Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd, Basel, Switzerland.
SO Bioorganic & medicinal chemistry, (1997 Dec) 5 (12) 2165-71.
Journal code: 9413298. ISSN: 0968-0896.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English

10813347

FS Priority Journals
EM 199804
ED Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980409
AB O-Methylasparvenone (1) and asparvenone (2) were isolated from an Aspergillus parvulus Smith broth in a microbial screening for **5-HT2C** ligands and found to be **5-HT2C antagonists.** They represent the first nitrogen-free serotonin ligands. The absolute configuration of 1 was determined to be S by X-ray analysis of the corresponding Mosher-ester. A short and efficient synthesis of rac-1 was developed. This protocol was applied to the synthesis of derivatives of 1 and a structure-affinity relationship was established.

L22 ANSWER 9 OF 16 MEDLINE on STN
AN 1998098697 MEDLINE
DN PubMed ID: 9436302
TI Structure and serotonin 5-HT2C receptor activity of ortho- and meta-substituted phenylpiperazines.
AU Verdonk M L; Voogd J W; Kanters J A; Kroon J; den Besten R; Brandsma L; Leysen D; Kelder J
CS Department of Crystal and Structural Chemistry, Bijvoet Center for Biomolecular Research, Utrecht University, The Netherlands.
SO Acta crystallographica. Section B, Structural science, (1997 Dec 1) 53 (Pt 6) 976-83.
Journal code: 8403252. ISSN: 0108-7681.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980217
Last Updated on STN: 19990129
Entered Medline: 19980204
AB The structural characteristics of ortho- and meta-substituted phenylpiperazines have been investigated in order to understand their actions at the serotonin **5-HT2C** receptor. The crystal structures of the 4-methylated analogues of two phenylpiperazines that are already known as **5-HT2C** ligands, 1-(1-naphthyl)-4-methylpiperazine (1NMP) and 1-[(3-trifluoromethyl)phenyl]-4-methylpiperazine (TFMPMP), and those of two novel **5-HT2C** ligands, 1-(2-methoxyphenyl)piperazine (oMPP) and 1-(3-methoxyphenyl)piperazine (mMPP), are determined. Molecular mechanics calculations are performed to calculate the energy profiles of six phenylpiperazines for rotation about the central phenyl-nitrogen bond. The activities of several phenylpiperazines, in combination with their crystal structures and conformational characteristics, lead to the hypothesis that the conformation for which the piperazine ring and the phenyl ring are approximately co-planar should be the **5-HT2C** receptor 'activating' conformation. This hypothesis is then used to predict the activities of the two novel **5-HT2C** ligands oMPP and mMPP. oMPP is predicted to be an **antagonist** at this receptor, whereas mMPP is predicted to be an agonist. As this prediction was confirmed by in vitro and in vivo tests, the proposed conformation is very likely to be responsible for the activation of the **5-HT2C** receptor.

L22 ANSWER 10 OF 16 MEDLINE on STN
AN 97447210 MEDLINE
DN PubMed ID: 9301661
TI Dihydrobenzofuran analogues of hallucinogens. 4. Mescaline derivatives.
AU Monte A P; Waldman S R; Marona-Lewicka D; Wainscott D B; Nelson D L; Sanders-Bush E; Nichols D E
CS Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907, USA.
NC DA02189 (NIDA)
DA05181 (NIDA)
SO Journal of medicinal chemistry, (1997 Sep 12) 40 (19) 2997-3008.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971021
Last Updated on STN: 19990129

10813347

Entered Medline: 19971008

AB Dihydrobenzofuran and tetrahydrobenzodifuran functionalities were employed as conformationally restricted bioisosteres of the aromatic methoxy groups in the prototypical hallucinogen, mescaline (1). Thus, 4-(2-aminoethyl)-6,7-dimethoxy-2,3-dihydrobenzofuran hydrochloride (8) and 1-(8-methoxy-2,3,5,6-tetrahydrobenzo[1,2-b:5,4-b']difuran-4-yl)-2-aminoethane hydrochloride (9) were prepared and evaluated along with 1 for activity in the two-lever drug discrimination (DD) paradigm in rats trained to discriminate saline from LSD tartrate (0.08 mg/kg). Also, 1, 8, and 9 were assayed for their ability to displace [3H]ketanserin from rat cortical homogenate 5-HT2A receptors and [3H]8-OH-DPAT from rat hippocampal homogenate 5-HT1A receptors. In addition, these compounds were evaluated for their ability to compete for agonist and **antagonist** binding to cells expressing cloned human 5-HT2A, 5-HT2B, and **5-HT2C** receptors. Finally, agonist efficacy was assessed by measurement of phosphoinositide hydrolysis in NIH 3T3 cells expressing the rat 5-HT2A or **5-HT2C** receptors. Although 1 fully substituted for LSD in the DD assays (ED50 = 33.5 mumol/kg), neither 8 nor 9 substituted for LSD, with just 50% of the rats administered 8 selecting the drug lever, and only 29% of the rats administered 9 selecting the drug lever. All of the test compounds had micromolar affinity for the 5-HT1A and 5-HT2A receptors in rat brain homogenate. Curiously, the rank order of affinities of the compounds at 5-HT2A sites was opposite their order of potency in the behavioral assay. An evaluation for ability to stimulate phosphoinositide turnover as a measure of functional efficacy revealed that all the compounds were of approximately equal efficacy to serotonin in **5-HT2C** receptors. At 5-HT2A receptors, however, 8 and 9 were significantly less efficacious, eliciting only 61 and 45%, respectively, of the maximal response. These results are consistent with the proposed mechanism of action for phenethylamine hallucinogens, that such compounds must be full agonists at the 5-HT2A receptor subtype. In contrast to the 2,5-dimethoxy-substituted phenethylamines, where rigidification of the methoxy groups had no deleterious effect on activity, the loss of activity in the 3,4,5-trioxygenated mescaline analogues may suggest that the 3 and 5 methoxy groups must remain conformationally mobile to enable receptor activation.

L22 ANSWER 11 OF 16 MEDLINE on STN
AN 96408626 MEDLINE
DN PubMed ID: 8813633
TI Molecular modeling of serotonin, ketanserin, ritanserin and their 5-HT2C receptor interactions.
AU Kristiansen K; Dahl S G
CS Department of Pharmacology, Institute of Medical Biology, University of Tromso, Norway.
SO European journal of pharmacology, (1996 Jun 13) 306 (1-3) 195-210. Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961218

AB Molecular modeling techniques were used to build a three-dimensional model of the rat **5-HT2C** receptor, which was used to examine receptor interactions for protonated forms of serotonin, ketanserin and ritanserin. Molecular dynamics simulations which were started with the fluoro benzene moiety of ketanserin and ritanserin oriented towards the cytoplasmic side of the receptor model, produced the strongest **antagonist**-receptor interactions. The fluoro bezene ring(s) of the **antagonists** interacted strongly with aromatic residues in the receptor model, which predicts slightly different orientations and ligand-receptor interactions of ketanserin and ritanserin at a putative binding site. The model suggests that Asn333 (transmembrane helix 6) is involved in a hydrogen-bonding interaction with ketanserin, but not with ritanserin. The model also also suggests that the position corresponding to Cys362 (transmembrane helix 7) may be an important determinant for specifying 5-HT2A receptor selectivity in ketanserin binding.

L22 ANSWER 12 OF 16 MEDLINE on STN
AN 96405021 MEDLINE
DN PubMed ID: 8809161
TI Serotonin 5-HT2 receptor, dopamine D2 receptor, and alpha 1 adrenoceptor antagonists. Conformationally flexible analogues of the atypical antipsychotic sertindole.

10813347

AU Andersen K; Liljefors T; Hyttel J; Perregaard J
CS Research Department, H. Lundbeck A/S, Copenhagen, Denmark.
SO Journal of medicinal chemistry, (1996 Sep 13) 39 (19) 3723-38.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199611
ED Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961104
AB Conformationally flexible analogues of the atypical antipsychotic sertindole (1-[2-[4-[5-chloro -1-(4-fluorophenyl)-1H-indol-3-yl]-4-piperidinyl]ethyl]-2-imidazolidi non e) were synthesized. Replacement of the 4-piperidinyl ring in sertindole by a 2-(methylamino)ethoxy group or a 2-(methylamino)ethyl group (e.g. 1-[2-[2-[5-chloro-1-(4-fluorophenyl)-1H -indol-3-yloxy]ethyl-methylamino]ethyl]-2-imidazolidinone and 1-[3-[[2-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl] -ethyl]methylamino]propyl]-2-imidazolidinone results in binding affinities for serotonin 5-HT2A and dopamine D2 receptors, as well as alpha 1 adrenoceptors, which are very similar to those of sertindole. (Methylamino)alkyl groups of other chain lengths, 3-(methylamino)propyloxy groups, and 2-(methylamino)ethylsulfanyl groups do not have such properties. The capability of the 2-(methylamino)ethoxy group and the 2-(methylamino)ethyl group to replace the 4-piperidinyl ring in sertindole is reflected in molecular modeling studies using recently published receptor-interaction models for 5-HT2 and D2 receptors. Structure-affinity investigations concerning the substituents in the indole nucleus and the 2-imidazolidinone ring system in the 2-(methylamino)ethoxy and the 2-(methylamino)ethyl analogues of sertindole have led to high affinity serotonin 5-HT2A receptor **antagonists** with selectivity versus dopamine D2 receptors and alpha 1 adrenoceptors (e.g. 1-[2-[[2-[6-chloro-1-(4-fluorophenyl) -1H-indol-3-yloxy]ethyl]methylamino]-ethyl]-2-imidazolidinone and 1-[3-[[2-[6-chloro-1-(4-fluorophenyl) -1H-indol-3-yl]ethyl]methylamino]propyl]-2-imidazolidinone). The latter derivative has also high selectivity for 5-HT2A receptors versus serotonin **5-HT2C** receptors. Replacement of the basic amino group by nitrogen-containing six-membered rings has led to 5-chloro-1-(4-fluorophenyl)-3-[(4-methylpiperazinyl)-ethoxy]-1H-in dole, which has high affinity for dopamine D2, versus low affinity for serotonin 5-HT2A receptors and alpha 1 adrenoceptors.

L22 ANSWER 13 OF 16 MEDLINE on STN
AN 96298060 MEDLINE
DN PubMed ID: 8709108
TI Potent, selective tetrahydro-beta-carboline antagonists of the serotonin 2B (5HT2B) contractile receptor in the rat stomach fundus.
AU Audia J E; Evrard D A; Murdoch G R; Droste J J; Nissen J S; Schenck K W; Fludzinski P; Lucaites V L; Nelson D L; Cohen M L
CS Lilly Research Laboratories, Division of Eli Lilly & Company, Indianapolis, Indiana 46285, USA.
SO Journal of medicinal chemistry, (1996 Jul 5) 39 (14) 2773-80.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
ED Entered STN: 19960919
Last Updated on STN: 19990129
Entered Medline: 19960910
AB A series of potent, selective 5HT2B receptor **antagonists** has been identified based upon yohimbine, with SAR studies resulting in a 1000-fold increase in 5HT2B receptor affinity relative to the starting structure (-log KBS > 10.0 have been obtained). These high-affinity tetrahydro-beta-carboline **antagonists** are able to discriminate among the 5HT2 family of serotonin receptors, with members of the series showing selectivities of more than 100-fold versus both the 5HT2A and **5HT2C** receptors based upon radioligand binding and functional assays. As the first compounds reported with such selectivity and enhanced receptor affinity, these tetrahydro-beta-carboline **antagonists** are useful tools for elucidating the role of serotonin acting at the 5HT2B receptor in normal and disease physiology.

L22 ANSWER 14 OF 16 MEDLINE on STN
AN 96250454 MEDLINE
DN PubMed ID: 8692282

10813347

TI Evidence for presynaptic location of inhibitory 5-HT1D beta-like autoreceptors in the guinea-pig brain cortex.
AU Buhlen M; Fink K; Boing C; Gothert M
CS Institut fur Pharmakologie und Toxikologie, Universitat Bonn, Germany.
SO Naunyn-Schmiedeberg's archives of pharmacology, (1996 Feb) 353 (3) 281-9.
Journal code: 0326264. ISSN: 0028-1298.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199608
ED Entered STN: 19960911
Last Updated on STN: 19960911
Entered Medline: 19960823
AB The effects of 5-hydroxytryptamine (5-HT) receptor agonists and **antagonists** on tritium overflow evoked by high K+ were determined in superfused synaptosomes and slices, preincubated with [3H]5-HT, from guinea-pig brain cortex. In addition, we estimated the potencies of 5-HT receptor ligands in inhibiting specific [3H]5-HT binding (in the presence of 8-hydroxy-2(di-n-propylamino)tetralin and mesulergine to prevent binding to 5-HT1A and **5-HT2C** sites) to guinea-pig cortical synaptosomes and membranes. 5-HT receptor agonists inhibited the K(+)-evoked tritium overflow from synaptosomes and slices. In synaptosomes the rank order of potencies was 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl] -1H-indole-3-yl] ethylamine (L-694,247) > 5-carboxamidotryptamine (5-CT) > oxymetazoline (in the presence of idazoxan) > or = 5-HT > sumatriptan > or = 5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (RU 24969). The potencies of the agonists in inhibiting tritium overflow from slices correlated with those in synaptosomes, suggesting that the same site of action is involved in both preparations. In synaptosomes the nonselective **antagonist** at cloned human 5-HT1D alpha and 5-HT1D beta receptors, methiothepin, shifted the concentration-response curve for 5-CT to the right (apparent pA2: 7.87). In contrast, ketanserin at a concentration which should block the 5-HT1D alpha, but not the 5-HT1D beta, receptor did not alter the inhibitory effect of 5-CT on tritium overflow. In cortical synaptosomes and membranes, [3H]5-HT bound to a single site with high affinity. In competition experiments, 5-HT receptor agonists and **antagonists** inhibited specific [3H]5-HT binding. In synaptosomes the rank order was L-694,247 > methiothepin > 5-CT > 5-methoxytryptamine > 5-HT > or = sumatriptan > or = oxymetazoline > RU 24969 > ketanserin > ritanserin. A very similar rank order was obtained in cerebral cortical membranes. The potencies of the 5-HT receptor agonists in inhibiting tritium overflow from synaptosomes and slices correlated with their potencies in inhibiting [3H]5-HT binding to synaptosomes and membranes. In conclusion, the 5-HT receptors mediating inhibition of 5-HT release in the guinea-pig cortex are located on the serotoninergic axon terminals and, hence, represent presynaptic inhibitory autoreceptors. The [3H]5-HT binding sites in cerebral cortical synaptosomes and membranes exhibit the pharmacological properties of 5-HT1D receptors. The correlation between the functional responses and the binding data confirms the 5-HT1D character of the presynaptic 5-HT autoreceptors. According to the results of the interaction experiment of ketanserin and methiothepin with 5-CT on 5-HT release, the presynaptic 5-HT autoreceptors can be subclassified as 5-HT1D beta-like.

L22 ANSWER 15 OF 16 MEDLINE on STN
AN 96028198 MEDLINE
DN PubMed ID: 7473556
TI (+/-)-(N-alkylamino)benzazepine analogs: novel dopamine D1 receptor antagonists.
AU Shah J H; Izenwasser S; Geter-Douglass B; Witkin J M; Newman A H
CS Psychobiology Section, National Institutes of Health, National Institute on Drug Abuse-Division of Intramural Research, Baltimore, Maryland 21224, USA.
SO Journal of medicinal chemistry, (1995 Oct 13) 38 (21) 4284-93.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199511
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951128
AB (+/-)-(N-Alkylamino)benzazepine analogs were prepared as novel dopamine D1 receptor **antagonists** to further elucidate the role of these receptor subtypes in the pharmacology and toxicology of cocaine. In the

first series of compounds, (+/-)-7-chloro-8-hydroxy-3-[6-(N,N-dimethylamino)-hexyl]-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (15) showed the highest affinity (Ki = 49.3 nM) and subtype-selectivity for dopamine D1 over dopamine D2, 5-HT2a, and **5-HT2c** receptors. Compounds 7a [(+/-)-7-Chloro-8-hydroxy-3-[4-(N,N-dimethylamino)butyl]-1-phenyl- 2,3,4,5-tetrahydro-1H-3-benzazepine], 11 [(+/-)-7-chloro-8-hydroxy-3-[6-[(N,N-dimethylamino)hexyl]-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-cyanoborane], and 15 were moderately potent dopamine D1 receptor **antagonists** as evidenced by their ability to block dopamine-stimulated adenylyl cyclase activity in rat caudate (predicted Ki values = 60, 34, and 21 nM, respectively). Compound 7a appears to be unique in that, despite its relatively potent inhibition of dopamine stimulated adenylyl cyclase, it demonstrated relatively weak binding affinity at the dopamine D1 receptors (Ki = 811 nM). Unlike previously reported N-alkylbenzazepines, where a significant loss in dopamine D1 receptor binding affinity was observed when successive increases in the alkyl side chain size at the benzazepine nitrogen were made, several of these novel N-alkylamino analogs demonstrated high-affinity binding with an optimal chain length of six carbons. This initial series of compounds appears to be identifying another binding domain on the dopamine D1 receptor protein that has not previously been characterized and that accepts an amino function. Further, these compounds may serve as templates for the design of peripherally active dopamine D1 receptor **antagonists.**

L22 ANSWER 16 OF 16 MEDLINE on STN
AN 95222530 MEDLINE
DN PubMed ID: 7707322
TI Ketanserin analogues: the effect of structural modification on 5-HT2 serotonin receptor binding.
AU Ismaiel A M; Arruda K; Teitler M; Glennon R A
CS Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virgina, Virginia Commonwealth University, Richmond 23298, USA.
SO Journal of medicinal chemistry, (1995 Mar 31) 38 (7) 1196-202.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199505
ED Entered STN: 19950518
Last Updated on STN: 19950518
Entered Medline: 19950511
AB Ketanserin (1) is a fairly selective 5-HT2 **antagonist** that binds both at 5-HT2A and **5-HT2C** receptors. A previous structure-affinity relationship study revealed that the structure of the piperidine-containing ketanserin molecule could be rather severely abbreviated with little effect on 5-HT2A affinity. The present investigation explores several inconsistencies identified in the earlier study and suggests that multiple modes of binding may be possible for ketanserin analogues. Perhaps the nature of the benzylic substituent is the most significant determinant of the manner in which these agents bind at 5-HT2A receptors, and it is possible that certain orientations may avail themselves of an auxiliary binding site. Depending upon the length of the piperidine N-alkyl chain, variation of the benzylic substituent from a carbonyl, to an alcohol, to a methylene group has a nonparallel influence on binding, and this may be further affected by the presence of a second ring nitrogen atom. The results of the present investigation provide evidence that although the structure of ketanserin can be abbreviated, and even modified by conversion of the piperidine ring to a piperazine, the resultant analogues may bind in more than one orientation at the receptors. A key structural feature that may play a prominent role in anchoring or orienting these compounds at 5-HT2A receptors is the benzylic carbonyl group.